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OCTOBER 1954

HUMAN SERUM LIPOPROTEIN CONCENTRATIONS
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ROGRAM OF THE DIVISIONS OF PSYCHOLOGICAL AND SOCIAL SCIENCES, CLINICAL MEDICINE, AND SOCIAL WORK AND ADMINISTRATION, SEVENTH ANNUAL SCIENTIFIC MEETING OF THE GERONTOLOGICAL SOCIETY, INC., IN COOPERATION WITH THE FIFTH ANNUAL SOUTHERN CONFERENCE OF THE INSTITUTE OF GERONTOLOGY OF THE UNIVERSITY OF FLORIDA AND ABSTRACTS OF PAPERS TO BE PRESENTED

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JOURNAL OF GERONTOLOGY

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HUMAN SERUM LIPOPROTEIN CONCENTRATIONS

FRANK W. GLAZIER, A.B., ARTHUR R. TAMPLIN, A.B., BEVERLY STRISOWER, A.B., OLIVER F. DeLALLA, A.B., JOHN W. GOFMAN, M.D., THOMAS R. DAWBER,[1] M.D., and EDWARD PHILLIPS,[2] M.D.

(From the Donner Laboratory, Division of Medical Physics, Department of Physics, and the Radiation Laboratory, University of California, Berkeley)

THE metabolism of lipids in the human is associated with a blood transport phase involving an entire series or "spectrum" of lipoproteins. There is considerable variability within the human population both in the total serum levels of lipoproteins and in the distribution among the various individual classes habitually present. Certain of these lipoproteins are of especial interest in the study of human atherosclerosis and in a variety of metabolic disorders.

The lipoproteins known to exist in human serum have been characterized in terms of their flotation rates in an intense centrifugal field. Broadly two major classes of lipoproteins are recognized, the "low density" lipoproteins and the "high density" lipoproteins. The methodology for the ultracentrifugal characterization and quantitation of both groups has been described in detail (1, 5). The high density group of lipoproteins comprise 3 species, one of density 1.05 Gm./ml., one of density 1.075 Gm./ml., and a third of 1.145 Gm./ml. The levels of these encountered in the population are described elsewhere (2).

Submitted for publication April 30, 1954.

This work was supported in part by the United States Atomic Energy Commission, the National Heart Institute of the United States Public Health Service, and the Lederle Laboratories Division of the American Cyanamid Corporation.

[1]Director, Framingham Heart Epidemiology Study, National Heart Institute, National Institutes of Health, United States Public Health Service.

[2]Consultant, Los Angeles City Health Department, and Department of Medicine, College of Medical Evangelists, Los Angeles, California.

This report is concerned especially with the serum levels, both in fasting and non-fasting subjects, of the "low density" group of lipoproteins. In a sodium chloride solution of density 1.063 Gm./ml. at 26°C. the "low density" lipoproteins undergo flotation with rates between S_f4 and $S_f40{,}000$ units. Between these limits exist a host of species of flotation rates so closely spaced as to render it difficult to choose between a continuum of lipoproteins between these limits or a series of discrete, but difficultly resolved, species.

The quantitation of any particular single lipoprotein species at a single flotation rate is not feasible at this time. It is possible, however, to measure the sum of concentrations of lipoproteins between two specified flotation rate limits, e.g., between S_f100 and S_f200. Measurements have been reported in the literature (3, 4) for the serum concentration of S_f12-20 and S_f20-100 classes of lipoproteins. In the last three years, however, such measurements have been extended and refined to include additional components, and more importantly to consider quantitatively a physico-chemical effect of the lipoproteins upon each other during ultracentrifugation. Lipoproteins, as well as other macromolecules, experience slowing of their ultracentrifugal migration rates as their concentration increases, and further the rate of migration of a particular lipoprotein class is decreased with increasing concentration of

all slower-floating species. A procedure for taking such slowing of flotation rate into account has been described by deLalla and Gofman (1) and has been in routine use in the authors' laboratory for the past three years. While compensating effects tended to correct for such slowing in the older reported values, it is our opinion that the occasional error introduced by the use of the older procedure is sufficient to warrant the use of the refined procedure with the concentration-slowing effects quantitatively taken into account.

In order to indicate that self-slowing and inter-lipoprotein slowing have been accounted for, the notation "Standard" has been applied to all the lipoprotein measurements. Thus reference has been made to the Standard S_f0-12, Standard S_f12-20, lipoprotein classes. The designation *standard* implies that the limits are placed such that the slowing effect of concentration itself has been taken into account. Thus if a particular lipoprotein is measured at some finite concentration its flotation rate will be less than its rate in an infinitely dilute solution. By correction for concentration it is assured that one is always referring to the same ultracentrifugally defined physico-chemical entity, whereas without such correction a particular species might at one concentration migrate at a certain flotation rate, whereas in a more concentrated solution its rate might be considerably reduced, leading to the erroneous conclusion that two different physico-chemical entities are involved.

The major purpose of this report is to provide the values for the serum concentration of several classes of lipoproteins measured by the refined procedure and hence designated by the Standard Flotation Rates, to serve as reference information for physiologic and pathologic studies. Measurements are available for 4 arbitrarily chosen lipoprotein classes, the Standard S_f0-12, Standard S_f12-20, Standard S_f20-100, and Standard S_f100-400 classes. For many studies we have found these 4 bands to represent a useful subdivision of the lipoprotein spectrum, especially in the study of human atherosclerosis, coronary heart disease, and various metabolic disorders. It should be emphasized that for special purposes one may find it desirable to combine certain of these subgroups, or to divide still further a particular class into further sub-classes. At present no data are available for the classes of lipoproteins between Standard S_f400 and Standard S_f40,000. To a large extent such measurements have been deferred because of the very high degree of variability of these highest classes of lipoproteins with respect to the time period relative to the ingestion of food.

In the presentation of population values for the serum levels of the various Standard flotation classes we have chosen to attempt a representation of the levels encountered in the population at a steady state, excluding only individuals with acute illnesses. The term "normal" has been so grossly misused and misinterpreted that it seems preferable to eliminate its usage here. Instead we shall refer to the levels encountered in samples of the population, with the nature of the sampling procedure described. Exclusions on such bases as the presence of elevated blood pressure, diabetes mellitus, asthma, peptic ulcer, gall bladder disease, syphilis, etc., will not be made, but rather such cases will represent the incidence of these findings in the population samples studied.[1] In connection with such problems as coronary heart disease or atherosclerosis, all such individuals constitute part of the substrate out of which coronary disease or clinical coronary atherosclerosis arise, and hence should be left in the population in the proportion in which they occur. Considerations of the serum lipoprotein levels in special disease entities can be made separately.

MATERIAL

Two major sources are represented in the population samples reported. First, in the

[1] Individuals with established overt coronary disease are excluded from the population. Their inclusion, taking into consideration their relative numbers, would not appreciably alter the lipoprotein distributions described herein for the population.

present investigation, 2,105 subjects studied by the Framingham Heart Project of the United States Public Health Service (National Heart Institute), provided a random cross section from the population of that community in the age range 30 to 70, the blood having been drawn at all intervals from morning through evening (non-fasting); second, 1,231 employees of the Los Angeles Civil Service Commission studied for the evolution of heart disease provided a random cross section from this population in the age range 40 to 70, the blood having been drawn in the morning from fasting individuals.[1] The sample of the population below 30 years of age constituted 222 individuals of the Berkeley University population plus a small sample (15) of clinically healthy children examined for routine purposes in a Pediatric Clinic, all of whom were non-fasting and drawn throughout the day.

[1] Whereas the results are presented as representative "fasting" and "non-fasting" population samples, it is true that there is a possibility that the geographic source difference may be of some significance.

Results and Discussion

The data for the various lipoprotein classes, including mean values, standard error of the mean, and standard deviation of the distributions are presented in tables 1-4 and are plotted in figures 1 and 2 for the 4 separately measured classes, Standard S_f0-12, Standard S_f12-20, Standard S_f20-100, and Standard S_f100-400, considered with respect to age, sex, and fasting or non-fasting state. Standard S_f12-400 is given in table 5.

Table 1. Mean Standard S_f0-12 Lipoprotein Levels

Mean Age	Fasting or Non-Fasting	No. of Cases	Mean Standard S_f0-12 (mg.%)	Standard Deviation of Distribution	Standard Error of Mean
		Males			
4.3	Non-fasting	9	312.5	.....	.....
16.2	Non-fasting	29	263.9	71.0	13.4
25.0	Non-fasting	75	302.0	81.3	9.4
35.1	Non-fasting	358	340.3	87.6	4.6
44.2	Non-fasting	313	363.8	84.4	4.8
44.4	Fasting	412	381.7	91.4	4.5
54.1	Non-fasting	228	367.4	89.4	5.8
54.3	Fasting	431	405.7	92.1	4.5
61.1	Non-fasting	43	360.2	79.1	12.1
63.2	Fasting	187	397.6	89.4	6.5
		Females			
5.0	Non-fasting	6	289.9	.....	.....
16.9	Non-fasting	32	271.0	80.4	15.5
23.5	Non-fasting	86	283.1	71.6	7.6
35.2	Non-fasting	452	304.0	75.7	3.6
44.0	Non-fasting	399	346.1	81.3	4.0
44.0	Fasting	105	351.7	81.1	8.1
53.9	Non-fasting	269	362.9	78.2	4.7
53.8	Fasting	68	388.4	74.8	9.2
61.5	Non-fasting	43	369.2	80.2	12.3
62.8	Fasting	28	426.0	108.0	20.8

TABLE 2. MEAN STANDARD S_f12-20 LIPOPROTEIN LEVELS

Mean Age	Fasting or Non-Fasting	No. of Cases	Mean Standard S_f12-20 (mg.%)	Standard Deviation of Distribution	Standard Error of Mean
		MALES			
4.3	Non-fasting	9	39.9	9.6	3.4
16.2	Non-fasting	29	36.5	20.8	3.9
25.0	Non-fasting	75	48.6	19.0	2.2
35.1	Non-fasting	358	61.8	28.4	1.5
44.2	Non-fasting	313	68.3	26.0	1.5
44.4	Fasting	412	75.7	30.5	1.5
54.1	Non-fasting	228	69.2	30.5	2.0
54.3	Fasting	431	82.7	31.1	1.5
61.1	Non-fasting	43	67.2	26.0	4.0
63.2	Fasting	187	78.4	32.5	2.4
		FEMALES			
5.0	Non-fasting	6	37.0	14.8	6.6
16.9	Non-fasting	32	38.1	18.4	3.3
23.5	Non-fasting	86	41.9	20.4	2.2
35.2	Non-fasting	452	53.5	30.9	1.5
44.0	Non-fasting	399	69.9	33.6	1.7
44.0	Fasting	105	70.1	35.8	3.5
53.9	Non-fasting	269	89.8	51.5	3.1
53.8	Fasting	68	92.5	42.3	5.2
61.5	Non-fasting	43	102.1	53.3	8.2
62.8	Fasting	28	106.4	48.2	9.2

TABLE 3. MEAN STANDARD S_f20-100 LIPOPROTEIN LEVELS

Mean Age	Fasting or Non-Fasting	No. of Cases	Mean Standard S_f20-100 (mg.%)	Standard Deviation of Distribution	Standard Error of Mean
		MALES			
4.3	Non-fasting	9	68.1	19.5	6.9
16.2	Non-fasting	29	66.5	28.7	5.4
25.0	Non-fasting	75	86.5	41.2	4.8
35.1	Non-fasting	358	101.0	48.8	2.6
44.2	Non-fasting	313	108.9	47.9	2.7
44.4	Fasting	412	105.5	56.2	2.8
54.1	Non-fasting	228	111.8	56.4	3.7
54.3	Fasting	431	106.2	57.1	2.8
61.1	Non-fasting	43	104.6	45.0	6.9
63.2	Fasting	187	100.1	53.8	3.9
		FEMALES			
5.0	Non-fasting	6	64.7	75.5	33.8
16.9	Non-fasting	32	52.4	24.2	4.4
23.5	Non-fasting	86	49.1	26.2	2.8
35.2	Non-fasting	452	63.6	34.3	1.6
44.0	Non-fasting	399	78.4	39.9	2.0
44.0	Fasting	105	64.1	37.6	3.7
53.9	Non-fasting	269	98.6	45.7	2.8
53.8	Fasting	68	82.9	44.1	5.4
61.5	Non-fasting	43	131.5	69.4	10.7
62.8	Fasting	28	105.3	65.9	12.7

TABLE 4. MEAN STANDARD S_f100-400 LIPOPROTEIN LEVELS

Mean Age	Fasting or Non-Fasting	No. of Cases	Mean Standard S_f100-400 (mg.%)	Standard Deviation of Distribution	Standard Error of Mean
		MALES			
4.3	Non-fasting	9	24.2	18.1	6.4
16.2	Non-fasting	29	28.2	23.1	4.4
25.0	Non-fasting	75	43.0	30.9	3.6
35.1	Non-fasting	358	73.5	79.5	4.2
44.2	Non-fasting	313	82.9	77.1	4.4
44.4	Fasting	412	49.5	58.2	2.9
54.1	Non-fasting	228	75.9	72.6	4.8
54.3	Fasting	431	44.4	48.8	2.4
61.1	Non-fasting	43	67.4	54.0	8.3
63.2	Fasting	187	42.1	46.8	3.4
		FEMALES			
5.0	Non-fasting	6	27.3	19.9	8.9
16.9	Non-fasting	32	14.1	11.2	2.0
23.5	Non-fasting	86	15.9	13.7	1.5
35.2	Non-fasting	452	25.8	27.1	1.3
44.0	Non-fasting	399	39.0	41.0	2.1
44.0	Fasting	105	23.1	19.9	2.0
53.9	Non-fasting	269	51.5	44.1	2.7
53.8	Fasting	68	29.8	19.9	2.4
61.5	Non-fasting	43	67.2	52.2	8.1
62.8	Fasting	28	42.8	34.0	6.5

TABLE 5. MEAN STANDARD S_f12-400 LIPOPROTEIN LEVELS

Mean Age	Fasting or Non-Fasting	No. of Cases	Mean Standard S_f12-400 (mg.%)	Standard Deviation of Distribution	Standard Error of Mean
		MALES			
4.3	Non-fasting	9	132.2	.....	.....
16.2	Non-fasting	29	131.3	63.6	12.4
25.0	Non-fasting	75	178.1	83.8	9.7
35.1	Non-fasting	358	236.1	135.0	7.2
44.2	Non-fasting	313	259.8	128.1	7.2
44.4	Fasting	412	230.7	117.3	5.8
54.1	Non-fasting	228	256.9	135.5	9.0
54.3	Fasting	431	233.0	112.9	5.5
61.1	Non-fasting	43	239.2	100.1	15.5
63.2	Fasting	187	220.6	109.1	8.1
		FEMALES			
5.0	Non-fasting	6	129.0	.....	.....
16.9	Non-fasting	32	104.8	43.5	9.6
23.5	Non-fasting	86	107.1	50.2	5.4
35.2	Non-fasting	452	142.9	77.7	3.6
44.0	Non-fasting	399	187.3	96.5	4.9
44.0	Fasting	105	157.2	80.2	7.8
53.9	Non-fasting	269	239.7	116.5	7.2
53.8	Fasting	68	205.2	88.9	10.8
65.1	Non-fasting	43	300.8	146.9	22.6
62.8	Fasting	28	254.2	125.7	24.2

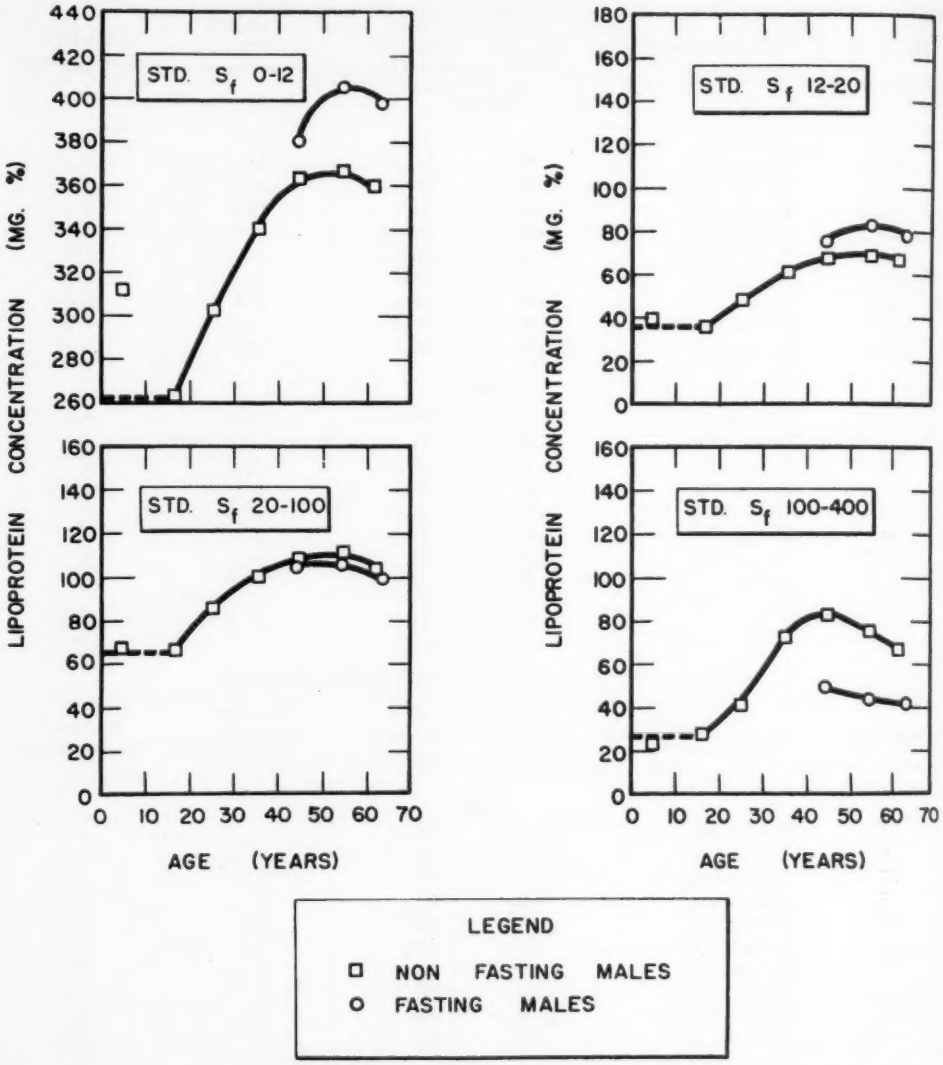

FIG. 1. The mean serum lipoprotein levels, including Standard S_f0-12, Standard S_f12-20, Standard S_f20-100, and Standard S_f100-400 classes, in men as a function of age. Values are plotted both for the fasting and non-fasting state.

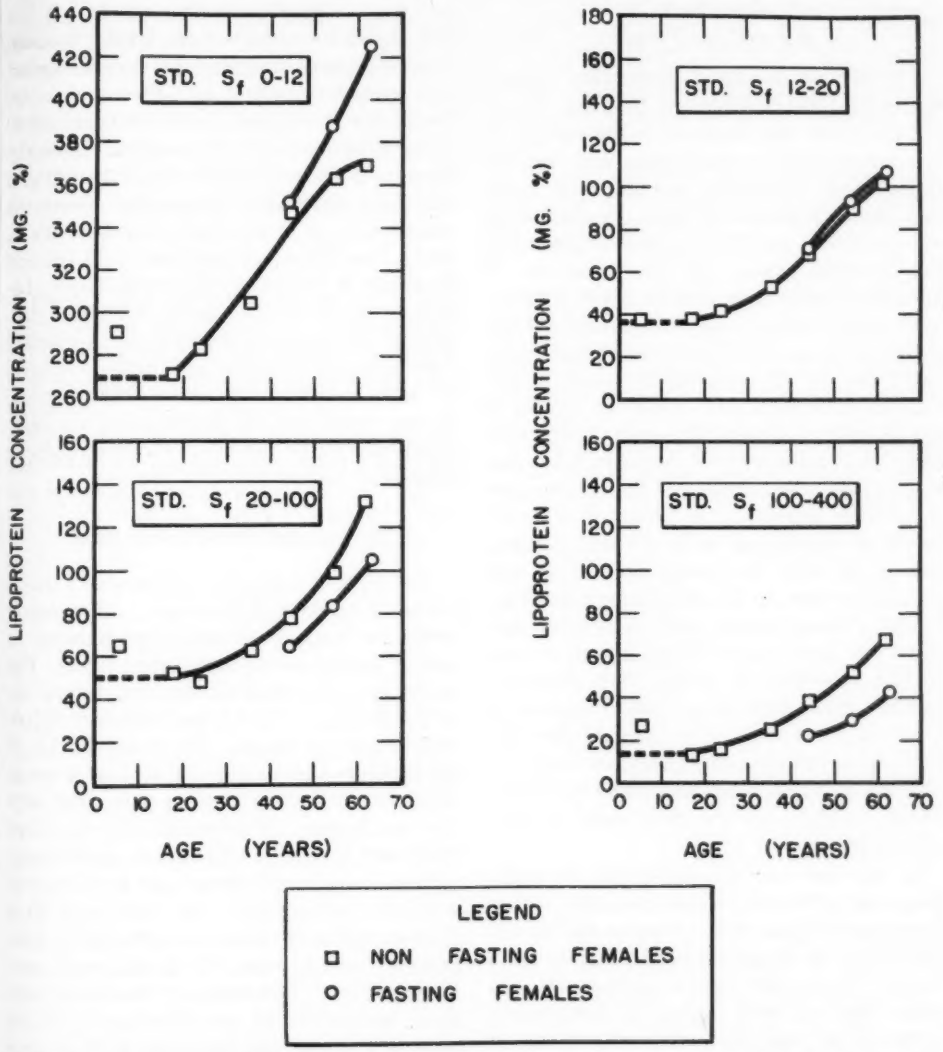

FIG. 2. The mean serum lipoprotein levels, including Standard S_f0-12, Standard S_f12-20, Standard S_f20-100, and Standard S_f100-400 classes, in women as a function of age. Values are plotted both for the fasting and non-fasting state.

Age and Sex Trends

For all the measured lipoprotein classes, Standard S_f0-12, Standard S_f12-20, Standard S_f20-100, and Standard S_f100-400, there is a general rise in mean lipoprotein concentration with increasing age, in both sexes, into the fifth decade of life. In the female sex the rising trend with age continues into the seventh decade. In the male sex all measured lipoprotein classes reach a maximum mean value in the fifth or sixth decade of life and then show a decrease in mean concentration of all lipoprotein classes in the sixth or seventh decades. From our studies of the relationships between serum lipoprotein levels and mortality from coronary heart disease, it would be anticipated that decimation of the male population will result in some removal of individuals with elevated lipoprotein levels with increasing age. This will account, in part, for the decreasing rate of increase in concentration with increase in age. However, from unpublished considerations of this question, it seems that mortality among individuals with high lipoprotein levels is not adequate to account for this effect in its entirety, and that there must exist an additional factor, metabolic in nature, which accounts for the male trend in lipoprotein levels.

In the first two decades of life no significant sex difference is demonstrable, within the limits of these data, either in the Standard S_f0-12 or Standard S_f12-20 lipoprotein levels. Beyond 20 years of age, however, the mean level of both classes is significantly higher in the male sex than in the female at least to the fifth decade of life, where the mean Standard S_f12-20 lipoprotein levels become equal in both sexes, and to the sixth decade of life, where the mean Standard S_f0-12 lipoprotein levels become equal. After the period when these lipoprotein classes become equal in mean levels for men and women, the mean level in women exceeds that in the men significantly at least through the seventh decade of life. The sex difference in Standard S_f20-100 and Standard S_f100-400 lipoprotein levels becomes manifest approximately one decade earlier, (i.e., second decade of life) than is the case for the Standard S_f0-12 and Standard S_f12-20 lipoprotein levels. Once manifest, the male-female difference in Standard S_f20-100 and Standard S_f100-400 lipoprotein levels is maintained up to the sixth decade of life at which time the mean Standard S_f20-100 and Standard S_f100-400 levels, respectively, become equal in the two sexes. Sufficient data beyond the period at which these lipoprotein classes become equal in level in the two sexes are not available to determine the sex trend in later years. At the present time the metabolic basis for the observed sex differences in lipoprotein levels remains obscure.

Fasting and Non-Fasting Levels

The data in tables 1-5 and figures 1 and 2 reveal significant differences in lipoprotein levels for both sexes and over a range of ages in fasting versus non-fasting blood. The major changes, observed for both sexes, are in the Standard S_f0-12 and Standard S_f100-400 lipoprotein classes. The Standard S_f0-12 lipoproteins show significently higher mean levels in the fasting state as compared with the non-fasting. Conversely, the Standard S_f100-400 lipoprotein levels are significantly higher in the non-fasting state as compared with the fasting state.[1] In both sexes there exists a region of minimum variation in lipoprotein level between the fasting and non-fasting state. This region of minimum variation seemed to be the Standard S_f20-100 class in the men and Standard S_f12-20 class in the women.

Since in the non-fasting individual it is primarily the lipoproteins of the high flotation rates (Standard S_f100-400) which are elevated, it would seem that these classes are those primarily involved in the early steps of the metabolism of exogenous foodstuff, probably largely fatty foodstuffs. In the fasting individual the elevation of Stand-

[1] A t test of significance of the difference in means for these variables reveals significance beyond the 1 per cent level.

ard S_f0-12 lipoproteins suggests that this class of lipoproteins is involved in a much later phase of the metabolism of exogenous fatty food. This in no way implies that endogenous fat does not utilize the same metabolic pathways. What is implied is the probable direction of "flow" of fat through the system of serum lipoproteins.

SUMMARY

The age and sex trends in the serum concentration of lipoproteins of the Standard S_f0-12, Standard S_f12-20, Standard S_f20-100, and Standard S_f100-400 classes have been measured.

Significant differences in serum lipoprotein levels are demonstrable between fasting and non-fasting subjects.

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LIPOPROTEINS, AGING, AND CORONARY ARTERY DISEASE

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CORONARY artery disease is in essence a chronic accumulative disease, rather than an acute process. Examination of the coronary arteries of the living population would reveal that there exists a continual gradation in the severity of the disease, wholly independent of whether or not clinical manifestations are present. A quantitative evaluation of coronary artery disease must take cognizance of these facts. Expressed succintly, these considerations indicate it will not be possible to devise any test involving the mass of the population which will separate out two groups designated as those with coronary disease and those without coronary disease. It therefore become obvious that any test which measures an individual's outlook with respect to coronary artery disease must be one which measures the extent to which the disease has progressed, since *existence* of the disease in the individual may be taken as axiomatic. The major purpose of this discussion is to present a method for the evaluation of an individual's degree of "accumulated coronary artery disease."

THEORETICAL ASPECTS OF THE CONCEPT OF ACCUMULATED CORONARY ARTERY DISEASE

It seems entirely reasonable that, if one can speak of accumulated coronary artery disease, there must exist a rate of accumulation of disease operating over some time period. If the rate of accumulation of disease varies at different periods in an individual's existence, then the total accumulated disease would be represented by the sum of each rate multiplied by the time over which each rate operated. A simple concept worthy of test is that the rate of accumulation is proportional to the magnitude of a causative factor, whatever this factor might be. Actual test of this concept demands some knowledge of the nature of this causative factor. Many features of coronary artery disease have for long suggested that the disease is in some way related to certain body lipid constituents. In particular evidence has accumulated (2, 3, 6) demonstrating a strong relationship between coronary artery disease and the concentration of certain serum lipoproteins. It is a reasonable hypothesis that the "effective" concentration of serum lipoproteins may represent the sought-for magnitude of the immediate causative factor or may be proportional to it. The term "effective" requires clarification. If all the lipoprotein classes in serum were equally involved in the disease, the effective concentration would be the sum of concentrations of individual lipoprotein classes. However, previous studies of this question (4, 5), indicated that the lipoproteins of the Standard $S_f12\text{-}400$ class are approximately 2 times as important for coronary disease as are the lipoproteins of the Standard $S_f0\text{-}12$ class. This evidence was the result of lipoprotein comparisons between groups of individuals with clinically manifest coronary artery disease and those without such manifest disease. The actual numerical evaluation of the relative importance of the two lipoprotein classes is sensitive to the difference in mean values of both classes between the manifestly diseased group and the group without manifest disease.

In the present work we have re-evaluated this relative importance factor, utilizing the manifestly-diseased group with the largest

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number of cases (50 to 59 year old men with clinical coronary artery disease) and the corresponding age and sex group among studied individuals without clinical coronary heart disease.[1] The application of the same statistical method previously applied, Fisher's linear discriminant analysis, to these groups of 50 to 59 year old men, yields the result that the Standard S_f12-400 lipoproteins are 1.6 times as important as the Standard S_f0-12 lipoproteins in segregating individuals with manifest coronary disease from those not showing clinically-overt disease. Very likely the increased effectiveness per unit concentration of Standard S_f12-400 lipoproteins as compared with Standard S_f0-12 lipoproteins reflects a similar situation with respect to the development of coronary disease. Returning now to the problem of effective concentration of the lipoproteins, the 1.6 fold importance factor may be taken into account by the following expressions:

Define α as the "effective" concentration of lipoproteins.

Write (Standard S_f0-12) = Concentration of Standard S_f0-12 lipoproteins.

Write (Standard S_f12-400) = Concentration of Standard S_f12-400 lipoproteins.

Then $\alpha = 0.1$ (Standard S_f0-12) + 0.16 (Standard S_f12-400).

Introducing this α value into the concept that rate of accumulation of coronary artery disease is *proportional* to the magnitude of the causative factor, we may write:

$$\text{Rate of Accumulation} = k \times \alpha$$

The constant k is a proportionality factor relating rate with effective concentration. In practice, application of this simple equation relating rate of accumulation of coronary disease to the α value would proceed as follows: If an individual were characterized by an effective concentration, α_1, for a period of ten years, he would at the end of the ten year period have accumulated ($k \times 10 \times \alpha_1$) units of coronary disease. If for the next ten year period he were characterized by an effective concentration, α_2, he would in this ten year period accumulate an additional ($k \times 10 \times \alpha_2$) units of coronary disease. In the total twenty year period considered, he would have accumulated ($k \times 10 \times \alpha_1 + k \times 10 \times \alpha_2$) total units of coronary disease. Generalization of this procedure would result by addition of all the increments of coronary disease from birth to a given age. In figure 1 is plotted the α value for a single individual over the first 60 years of life. Applying the reasoning above to successively smaller time intervals we arrive at the conclusion that by 60 years of age the total accumulated coronary disease = k x Area under the Curve. In the notation of elementary calculus, total accumulated coronary disease equals: $k \times \int_0^{60} \alpha \, dT$ since the area under the curve $= \int_0^{60} \alpha \, dT$. Since the units of accumulated coronary artery disease are arbitrary, it is

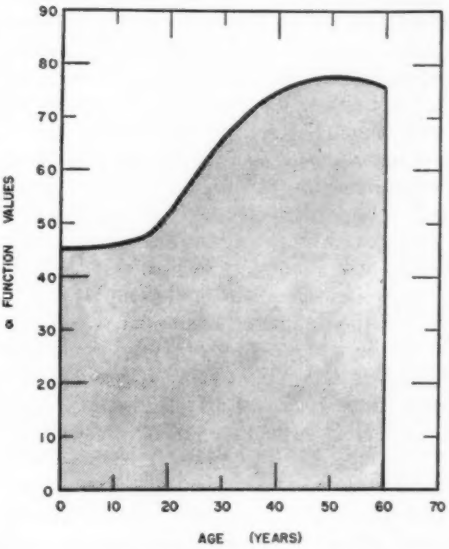

FIG. 1. This is a plot of the α value for the average man through the first sixty years of life. The crosshatched area divided by 10 out to any age gives the A.C.D. value for that age.

[1] The non-coronary group is represented by 50-50 combination of fasting and non-fasting individuals, since this most closely corresponds to the coronary population, with respect to fasting and non-fasting state. This differs from the non-coronary population chosen in reference (3). In that report a California population sample was utilized for best matching with the California coronary group, at a time when it was not realized that the California non-coronary group were all in the fasting state at the time of sampling.

most convenient to so choose them such that $k = 1/10$

Then we may write:

Accumulated Coronary Disease $= 1/10$ x Area Under the Curve $= 1/10 \int \alpha \, dT$. Henceforth accumulated coronary disease will be referred to as A.C.D., where it will be implicitly understood that:

$$\text{A.C.D.} = \frac{\text{Area Under the Curve of } \alpha \text{ plotted against T}}{10} = 1/10 \int \alpha \, dT.$$

The validity of this entire hypothesis concerning accumulation of coronary disease must be tested. If it were possible to measure by independent methods the actual rate of development of coronary disease or the total accumulated coronary disease up to any particular age, it would be possible to evaluate the hypothesis directly. But no such independent method of measurement exists, to our knowledge. There is, however, a satisfactory indirect method for testing the hypothesis. Excellent evidence exists (1, 7, 8) that the extent of accumulated coronary artery disease is closely related to clinical manifestations of coronary disease and to death from coronary artery disease. From A.C.D. measurements alone it is readily possible to predict incidence rates of clinical manifestations of coronary disease and thence mortality rates from coronary disease. These predicted mortality rates can be tested against established actuarial data.

We may consider two groups, first, a population of individuals without overt coronary disease and, second, the population of individuals in whom, out of the first group, coronary disease develops, for both groups of which A.C.D. values have been measured.[1] For a particular A.C.D. value suppose there are 100 individuals in the original group and that one of these individuals develops coronary disease in a time period of one year. Then the incidence rate per year of developing overt coronary disease at that A.C.D. value is 1/100. Similarly for any other A.C.D. value the incidence rate of developing overt coronary disease is the number of individuals who develop coronary disease at that A.C.D. value divided by the total number of individuals with that A.C.D. value in the original group. This allows the construction of a scale of incidence rates of development of coronary disease in relation to A.C.D. values.

Such a scale of relative incidence rates has been constructed from experimentally measured A.C.D. values. The distribution of A.C.D. values in individuals without overt

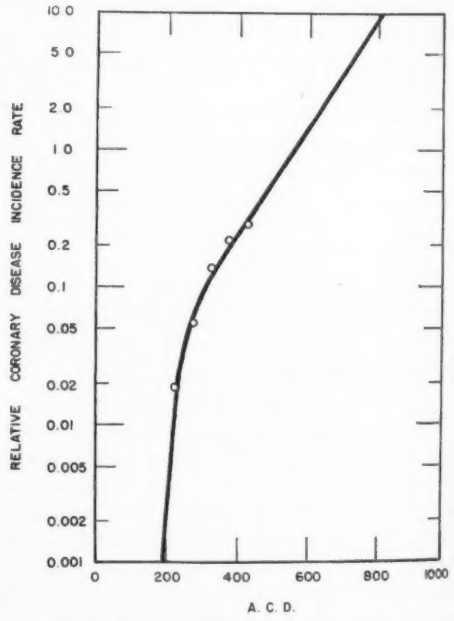

FIG. 2. Relative Coronary Disease Incidence Rate plotted as a function of A.C.D. values (accumulated coronary disease values). This curve is based upon the distribution of A.C.D. values in the non-coronary and coronary populations studied (see text for derivation).

[1] The A.C.D. values for these groups are obtained by the area integration procedure described above for a group of individuals without manifest disease and a group of individuals with overt coronary disease. For each individual in such groups the reasonable approximation is made that his position on a scale of α values remains the same relative to his fellows throughout life (See reference 3).

coronary disease is that for men and women between 30 to 69 years of age, combined in such proportions as to give a composite group comparable to the living population in the United States in this age range.[1] The A.C.D. values for individuals with coronary disease are those obtained for our entire sample with documented myocardial infarction, including men and women in the 30 to 69 year age range. Relative incidence rates at various A.C.D. values, calculated by the method described above, were obtained from these data and are plotted in figure 2.

Had the coronary group studied represented deaths from coronary disease, instead of existence of coronary disease in living individuals, the plot in figure 2 would have been relative mortality rates from coronary disease in relation to A.C.D. value. If we make the reasonable approximation that mortality rate from coronary disease is proportional to incidence rate of coronary disease, the curve plotted in figure 2 may be directly used to calculate relative mortality rates in relation to A.C.D. values. To calculate the mean mortality rate, or simply the mortality rate, for a particular population, the standard procedure for finding the mean is to sum up the value involved (mortality rate in this case) for each individual in the group and to divide by the total number of individuals. In table 1 are listed the distributions of A.C.D. values in our population samples of men and women considered by ten year age intervals for the range 30 to 69 years, and in addition the predicted relative mortality rates from coronary disease (evaluated from figure 2) for the midpoint of each

[1] The appropriate combining proportions were obtained from vital statistics data on the composition of the United States population (1949 data).

TABLE 1. DISTRIBUTION OF A.C.D. VALUES IN POPULATION SAMPLES AND THE CORRESPONDING PREDICTED RELATIVE CORONARY MORTALITY RATE

Range of A.C.D. Values	Number of Individuals in Each A.C.D. Range								Corresponding Predicted Relative Coronary Mortality Rate
	Men				Women				
	30-39 Years	40-49 Years	50-59 Years	60-69 Years	30-39 Years	40-49 Years	50-59 Years	60-69 Years	
0–50	0	0	0	0	0	0	0	0	
50–100	17	0	0	0	33	1	0	0	<0.00001
100–150	95	12	2	0	155	47	4	0	0.00001
150–200	112	57	10	2	106	105	41	5	0.0003
200–250	72	91	34	6	49	88	56	18	0.011
250–300	41	77	53	19	23	46	65	59	0.062
300–350	10	47	58	26	7	18	55	54	0.115
350–400	7	19	47	38		8	21	13	0.185
400–450	4	10	30	34		3	11	15	0.300
450–500		0	10	22		0	7	5	0.480
500–550		1	8	9		1	2	3	0.720
550–600		1	6	9				5	1.150
600–650			1	9				3	1.900
650–700				2					3.00
700–750				1					4.60
750–800				0					7.50
800–850				1					12.00
Total	358	315	259	178	372	317	262	180	
Mean Age in Years	35.1	44.3	54.2	62.1	35.2	44.0	53.9	62.1	

A.C.D. range encountered. The relative coronary disease mortality rates for the various subsegments of the population estimated in this way (from table 1) are given in table 2

TABLE 2. COMPARISON OF PREDICTED CORONARY DISEASE MORTALITY RATES WITH THOSE FROM U. S. VITAL STATISTICS[1]

	Mortality Rates from U. S. Vital Statistics	Predicted Mortality Rates from A.C.D. values
MEN		
35.1 years	0.27	0.32
44.3 years	1.00	1.00
54.2 years	3.39	2.94
62.1 years	6.73	7.99
WOMEN		
35.2 years	0.06	0.12
44.0 years	0.26	0.46
53.9 years	1.06	1.41
62.1 years	2.97	2.94

[1] United States Vital Statistics Tables, 1949 data.

together with the United States Vital Statistics Data[1] on Mortality. In order to bring both the predicted and the vital statistics mortality rates on to the same scale of relative values, the mortality rates for one group (arbitrarily chosen as the 44.3 year old men) were set at unity.

The general agreement between the mortality rates predicted solely upon A.C.D. values and those obtained from vital statistics is striking. The over-all quantitative aspects of the age and sex trends in coronary disease mortality are predicted well from A.C.D. values. First, the higher mortality in men as compared with women is predicted. Second, the rate of increase in mortality with increasing age is essentially in complete quantitative agreement for men, and except for slightly high prediction in the youngest groups, is also in quantitative agreement for women. Certainly, within the framework of the experimental data upon which the predictions are necessarily based, the observed agreement with vital statistics data may be considered to support the hypothesis of the relationship of the concept of accumulated coronary disease, as derived from lipoprotein measurements, with the clinical occurrence of coronary disease.

A first-order concept of the nature of the quantitative evolution of coronary disease is thus available. Second-order refinements are to be anticipated. Probably the most important such refinement will be a determination of the precise magnitude of the independent contribution of the blood pressure in coronary disease. Elsewhere evidence was presented (3) that the diastolic blood pressure is involved in coronary disease and is, in part at least, so involved independent of its interrelationship with serum lipoproteins. The best approach to the quantitative integration of the blood pressure findings into the concept of "accumulated coronary disease" is now being evaluated.

SOME CLINICAL IMPLICATIONS OF THE CONCEPT OF ACCUMULATED CORONARY ARTERY DISEASE

From one type of measurement, namely, serum lipoprotein determination, it now become possible to predict, for a particular individual of either sex and at any age, the quantitative outlook for the development of fatal coronary heart disease. Specifically, the physician would like to know the chance that a particular patient will develop fatal coronary disease at various future times, for example, one year, five years, or ten years after the date of examination. Such prediction data can be tabulated on the basis of the concept of accumulated coronary disease. The method employed is to measure the Standard S_f0-12 and Standard S_f12-400 lipoprotein classes ultracentrifugally. The α value is then calculated by the equation:

$$\alpha = 0.1\ (\text{Standard } S_f0\text{-}12) + 0.16\ (\text{Standard } S_f12\text{-}400)$$

By the method described earlier the A.C.D. value is obtained for this particular α value and the individual's age. From table 1 the

[1] The following categories of deaths in the Vital Statistics Tables have been considered to be representative of coronary artery disease: 420 (arteriosclerotic heart disease including coronary heart disease), 422 (other myocardial degeneration), 440-443 (hypertension with heart disease), (1949 Vital Statistics).

relative mortality rate for 44.3 year old men is calculated to be 0.0622. From vital statistics data the mortality rate estimated for coronary disease at 44.3 years is 180 per 100,000 per year. Therefore for each relative mortality rate in table 1, the absolute coronary mortality rate per year can be calculated for each A.C.D. value. Thus at any age and for a given α value (and hence A.C.D. value), the absolute coronary mortality rate can be determined. To calculate mortality rates for years beyond the year of measurement, the A.C.D. value for subsequent years is estimated by the approximation used previously that an individual's α value remains the same *relative* to his fellows. The mortality rates for the subsequent years are then obtained from figure 2. Utilizing these mortality rates, table 3 (sections 1-4) have been constructed which show, for men and women at various ages, the fraction of the population, at specified α values, that will be dead of coronary disease one year, five years, and ten years after the lipoprotein determination. In these calculations other causes of death have not been considered. There-

TABLE 3
CORONARY DISEASE MORTALITY IN RELATION TO AGE AND α VALUE

MEN (35 years of age)		Fraction of total number of individuals at each α value dead of coronary disease within:		
α value	A.C.D. value	1 year	5 years	10 years
20	57	0.000015	0.000085	0.00019
40	107	0.000028	0.00015	0.00034
60	157	0.000038	0.00081	0.00318
80	207	0.00015	0.00275	0.0105
100	257	0.00151	0.0105	0.0283
120	307	0.0028	0.0189	0.0495
140	357	0.0050	0.0340	0.0889
160	407	0.0077	0.0606	0.170
180	457	0.0131	0.0880	0.224
200	507	0.0160	0.132	0.357
MEN (45 years of age)				
20	93	0.000023	0.00012	0.00027
40	153	0.000038	0.00023	0.00056
60	213	0.00030	0.0033	0.0111
80	273	0.0019	0.0125	0.0321
100	333	0.0039	0.0253	0.0642
120	393	0.0065	0.0453	0.119
140	453	0.0125	0.0864	0.221
160	513	0.0208	0.155	0.391
180	573	0.0362	0.274	0.631
200	633	0.0640	0.438	0.837

TABLE 3—Continued
CORONARY DISEASE MORTALITY IN RELATION TO AGE AND α VALUE

MEN (55 years of age)		Fraction of total number of individuals at each α value dead of coronary disease within:		
α value	A.C.D. value	1 year	5 years	10 years
20	119	0.000029	0.00014	0.00029
40	195	0.000048	0.00025	0.00052
60	271	0.00185	0.0110	0.0165
80	347	0.0045	0.0279	0.0683
100	423	0.0093	0.0622	0.159
120	499	0.0176	0.133	0.343
140	575	0.0366	0.289	0.663
160	651	0.076	0.517	0.908
180	727	0.151	>0.752	>0.967
200	803	0.273	>0.879	>0.988
MEN (65 years of age)				
20	138	0.000035	>0.000175	>0.00035
40	243	0.0011	>0.0055	>0.011
60	348	0.0046	>0.0228	>0.0451
80	453	0.0125	>0.0609	>0.118
100	558	0.0326	>0.153	>0.282
120	663	0.083	>0.352	>0.579
140	768	0.218	>0.707	>0.915
160	872	0.400	>0.922	>0.994
180	978	>0.400	>>0.922	>>0.994
200	1083	>0.400	>>0.922	>>0.994

TABLE 3—(Continued)
CORONARY DISEASE MORTALITY IN RELATION TO AGE AND α VALUE

WOMEN (35 years of age)		Fraction of total number of individuals at each α value dead of coronary disease within:		
α value	A.C.D. value	1 year	5 years	10 years
20	58	0.000014	0.000084	0.000203
40	118	0.000029	0.000159	0.000355
60	178	0.000044	0.00123	0.00496
80	238	0.00103	0.00673	0.0173
100	298	0.00255	0.0153	0.0368
120	358	0.0050	0.0289	0.0672
140	418	0.0087	0.0495	0.113
160	478	0.0153	0.0874	0.197
180	538	0.0274	0.147	0.309
200	598	0.0420	0.230	0.473
WOMEN (45 years of age)				
20	85	0.000021	0.000118	0.000268
40	146	0.000036	0.000224	0.000558
60	207	0.00013	0.00239	0.00913
80	268	0.00178	0.0113	0.0285
100	329	0.0038	0.0228	0.0542
120	390	0.0064	0.0401	0.0985
140	451	0.0123	0.0757	0.181
160	512	0.0206	0.126	0.295
180	573	0.0362	0.218	0.476
200	634	0.065	0.373	0.722

TABLE 3—Continued
CORONARY DISEASE MORTALITY IN RELATION TO AGE AND α VALUE

WOMEN (55 years of age)		Fraction of total number of individuals at each α value dead of coronary disease within:		
α value	A.C.D. value	1 year	5 years	10 years
20	102	0.000025	0.00014	0.00031
40	170	0.000042	0.00106	0.00423
60	238	0.0011	0.0075	0.0171
80	306	0.0027	0.0174	0.0442
100	374	0.0057	0.0369	0.0933
120	442	0.0113	0.0741	0.186
140	510	0.0202	0.138	0.338
160	578	0.0374	0.250	0.563
180	646	0.073	0.444	0.822
200	714	0.130	0.643	0.950
WOMEN (65 years of age)				
20	98	0.000024	>0.00012	>0.00024
40	178	0.000044	>0.00022	>0.00044
60	258	0.00153	>0.00763	>0.0152
80	338	0.00415	>0.0206	>0.0407
100	418	0.0087	>0.0427	>0.0836
120	498	0.0176	>0.0850	>0.163
140	578	0.0374	>0.174	>0.317
160	658	0.081	>0.344	>0.570
180	738	0.170	>0.606	>0.845
200	818	0.297	>0.828	>0.970

fore the actual fraction of the population dead will always be greater than that shown in table 3 for coronary disease alone. The prognostic implications of elevated lipoprotein levels, and hence elevated α values, are self-evident in the tabulated mortality data.

There are further implications of the concept of accumulated coronary disease in the area of prevention and therapeutics. If prevention is to be approached by lowering the *rate* of accumulation of coronary disease, (lowering the α value), it would be imperative early in life to establish and maintain a lowered α value. Solely on the basis of rate alone, essentially no immediate improvement in the hazard of coronary disease can be anticipated by lowering the α value at a relatively advanced age, e.g., 60 years, because of the already accumulated coronary disease. However at this age, or any age, a lowering of the α value would be predicted to improve the outlook in successive years relative to that which would have existed without lowering of the α value. The possibility that the A.C.D. value itself can be lowered at any age has not yet been evaluated. Such a

lowering would be required if the *immediate* prognostic outlook were to improve.

Summary

1. A quantitative concept of the evolution of coronary artery disease in terms of *rate* of accumulation of disease and total accumulated coronary disease is presented.

2. Rate of development of coronary disease is considered to be proportional to the "effective concentration" of serum lipoproteins.

3. Accumulated coronary disease in any time interval is considered to be proportional to the product of rate of accumulation x the time interval.

4. The concept has been evaluated by comparison of predicted coronary mortality rates in relation to sex and age with observed mortality rates (from Vital Statistics data). The quantitative agreement found in this comparison supports the validity of the concept.

5. The prognosis for the development of fatal coronary artery disease over a 10 year period beyond the date of measurement of serum lipoprotein levels has been quantitatively evaluated.

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LYMPHOCYTES IN NORMAL EPIDERMIS OF YOUNG, OLDER MIDDLE-AGED, AND SENILE RATS[1]

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IN SEVERAL previous reports (5, 6, 7) the occurrence of lymphocytes in the normal epidermis has been described. Recently, this subject has been discussed by Andreasen (1, 2). A study on age changes in the skin of Wistar Institute rats (8), using specimens from each of 4 regions of the body from 25 animals, showed marked qualitative differences between the epidermis of young and middle-aged and that of middle-aged and senile rats. While observations specifically on the cell types in the epidermis were not made in this study, it was noted that lymphocytes and clear cells are present in all of the age-groups.

In a field of investigation which has received so little attention as that of the role and ultimate fate of the lymphocytes and clear cells in the epidermis, it seems well worth while to investigate the number, appearance, and location in the epidermis of these cells at different ages. The literature on age changes in the skin (13), while presenting many interesting and fruitful studies, does not contribute any knowledge to this particular field. Much of the work on aging skin has been concerned with the human subject. In human epidermis the lymphocytes and clear cells, while apparently always present, are not as conspicuous as in the thinner epidermis of the rat. The epidermis of small rodents is suited admirably for counts of lymphocytes and clear cells. The present work, therefore, is confined to the rat.

The migration of lymphocytes into epithelial layers is a well recognized phenomenon. In fact, one of the explanations for the loss of the enormous numbers of these cells which enter the circulation is their migration into the lumen of the digestive tract and subsequent excretion. Jassinowsky in a series of studies (15, 16, 17) demonstrated the emigration of polymorphonuclear leucocytes through the mucous membrane of the oral cavity and of lymphocytes through the mucous membrane of the intestinal tract along its entire length. He used the method of repeated irrigation with warm physiologic salt solution, later counting the cells and making smears from the solution.

Since it is admitted that lymphocytes are present in the epithelium and since there is a constant loss of a certain amount of epithelial lining, such a method might be subject to criticism as far as proving an actual emigration through the epithelium. From our own studies on sections we are inclined to believe that while some elimination of lymphocytes does occur through the intestinal lumen, it is minimal in amount, and that these cells play some important role *within* the epithelial layer.

Erf (14), on the basis of interesting experiments in which he removed the entire gastro-intestinal tract and still found a disappearance of intravenously injected lymphocytes, concluded that they are not lost by this route. Gastroenterectomized animals which survived 8 to 24 hours, in fact, showed a severe and persistent lymphopenia which Erf believes favors the hypothesis that many of the circulating lymphocytes reach the bloodstream from the wall of the alimentary canal, presumably from the lymphoid tissue beneath the epithelium. Thus the gastro-intestinal tract would be more a source of new lymphocytes than a site for their elimination.

Lymphatic tissue in general seems to be very active in producing small lymphocytes. These travel in the one-way pathway of the

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lymphatic vessels from the gastrointestinal tract, lymph nodes, spleen, and other sources to reach the thoracic duct and right lymphatic duct and to be emptied into the bloodstream in enormous numbers. It has been shown by Yoffey and Drinker (20) that only 1 out of every 30 lymphocytes entering the blood is a wanderer which has emigrated from blood to connective tissue, then back to peripheral lymph and so once more to the blood. The remaining 29 are new recruits, formed in the lymphatic tissue, from which they pass through the lymphatic vessels directly to the blood. A large enough number of thoracic lymphocytes alone enter the blood to replace those already there at least twice a day (19).

Such considerations present us with the intriguing but difficult question of what actually does become of these millions of lymphocytes. The existence of this unanswered question makes it even more important, it seems to us, to focus our attention on the behavior of lymphocytes in regions in which they have been little studied. Both the skin and the lymphoid tissue have received considerable attention from gerontologists but the lack of recognition of lymphocytes in the normal epidermis has left the field of possible relationship between these systems completely open.

Material and Methods

Twenty-two rats of the Wistar Institute Albino strain were used in the present study. Nine of these were young animals, 21 days of age, 2 were older middle-aged animals, 600 and 650 days of age, and 11 were senile, 900 days of age. The skin specimens were taken from the interscapular region, fixed in Bouin's fluid or in 10 per cent formalin, dehydrated, cleared, and embedded in paraffin. Sections were cut at 5μ. Several stains were employed for each specimen. Four slides, each with several sections, were stained with hematoxylin and eosin, 2 with Mallory's triple stain, and 2 with Heidenhain's iron hematoxylin.

As in the previous work on the animals of 300 days (6), a count was made of 1000 nuclei (cells) in the stratum germinativum of each animal. As in that work, also, the counts necessarily do not represent purely quantitative data but involve the classification of certain cells as lymphocytes, of others as clear cells, and of still others as what we have termed intermediate cells. While such a classification involves a subjective element, it seems the only method applicable in seeking some statistical data. A considerable degree of agreement on the criteria for these cell types had been reached by the authors and it is a very rare instance where one of them, working independently, would classify a cell in a category other than that chosen by the other for that particular cell.

Observations

21 Day Rats

The epidermis (figs. 1 and 5) consists of a stratum germinativum only a few cells thick and of a stratum corneum, the laminae of which seem to separate readily from one another. There is no stratum granulosum.

Study under the oil immersion objective reveals that the epidermis is not homogeneous in regard to the type of cell present. The great majority, about 85 per cent, are of the ordinary epidermal type. These are characterized by clear nuclei with one or two large and conspicuous nucleoli and by a cytoplasm which is stained more or less intensely and generally is lightly basophilic.

The next most abundant cell type is the "clear cell." This type constitutes over 8.9 per cent of the cells in the stratum germinativum (table 1). These are cells usually almost equal to the epidermal cells in size but with a very distinctive appearance. The cytoplasm is almost or entirely clear, occasionally somewhat opalescent. The nucleus is vesicular but usually lacks definitive nucleoli and the nuclear sap is darker than in the ordinary epidermal cells. There is no way in which one could say definitely by inspection of these cells in comparison with the epidermal cells whether they represent a type "sui generis." Nor would one be certain

TABLE 1. YOUNG, IMMATURE RATS
Data Obtained by Counts of 1,000 Cells Per Animal from Region of Back

Identification Number	Age in Days and Sex	Lympho-cytes	Intermediate Cells	Clear Cells	Total No. of Mitotic Figures
671	21 M	38	12	157	1
672	21 F	24	11	99	1
690	21 M	25	25	61	6
692	21 M	23	18	75	1
693	21 F	24	29	77	1
695	21 M	21	24	91	0
696	21 F	23	29	98	6
699	21 M	22	16	78	1
700	21 F	24	28	67	0

whether they should be considered as an integral part of the ectodermal epidermis or as wandering cells from the mesodermal dermis.

A third type of cell present in the epidermis is the small lymphocyte, which constitutes about 2.4 per cent of the total number of cells of the stratum germinativum, or about one-fourth as many as the number of clear cells. The appearance of the small lymphocytes here is very similar to that seen in epithelia in other parts of the body, as in the intestine (9, 10, 11, 12). The nucleus is spheroidal and rather densely basophilic. No nucleoli are visible. There usually is a clear area about the nucleus, varying considerably in dimensions, from a narrow rim up to the size of the cytoplasmic body of many of the clear cells. This area or body of the lymphocyte differs from that of the clear cell in possessing an even greater degree of clarity and never showing the opalescence seen in some of the clear cells.

Still another appearance is found in another group of cells, for about 2.1 per cent of the cells in the stratum germinativum in these animals we could not classify as either lymphocytes on the one hand nor clear cells on the other but believed that they should be placed in a group which we have called intermediate cells. These cells show a somewhat more vesicular nucleus then does a clear-cut lymphocyte and a change in the cytoplasm in the direction of the clear cell type.

The lymphocytes, intermediate cells, and clear cells are generaly in the basal layer, but there are exceptions to this rule. All of these cell types give indication of exerting pressure on neighboring cells (figs. 4 and 6) as though they either were pushing their way into the epidermis or their cytoplasmic bodies were expanding.

The general appearance of the specimens of skin is very similar as one passes from one microscopic field to another in studying the various sections from this particular region of the body.

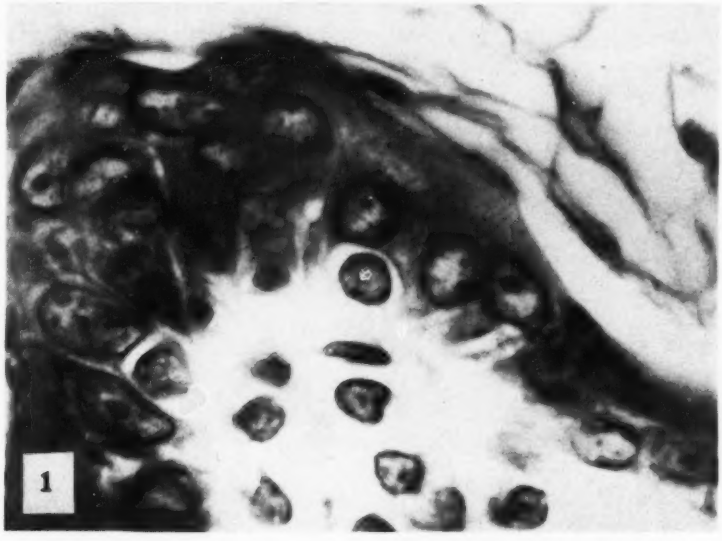
The dermis of the 21 day rats is richly cellular (fig. 1). The fibers appear as a delicate feltwork. There are many cells of a spheroid or ovoid shape, which probably are wandering cells, scattered among the fusiform and stellate fibroblasts.

600 to 900 Days Rats

In the older middle-aged and senile rats the epidermis consists of a stratum germinativum, a well-developed stratum granulosum, and a stratum corneum the laminae of which seem more closely adherent than in the young animals.

The ordinary epidermal cells differ somewhat in appearance from these cells in young rats in showing a more conspicuous cytoplasmic body. There is less of an aspect of crowding of the nuclei than seen in the young rats (figs. 2, 4, 7). The outstanding difference, however, is the conspicuous stratum granulosum, containing basophilic granules often of great size, in the senile animals.

In addition to the ordinary epidermal cells, the 3 types described for the 21 day rats are



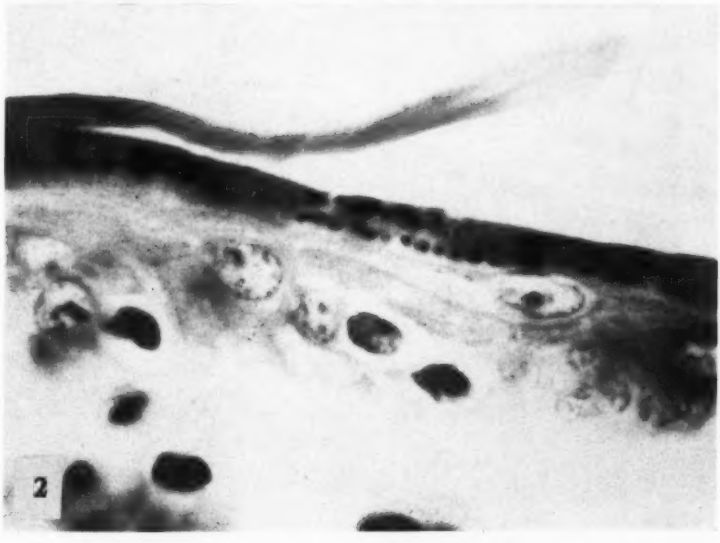
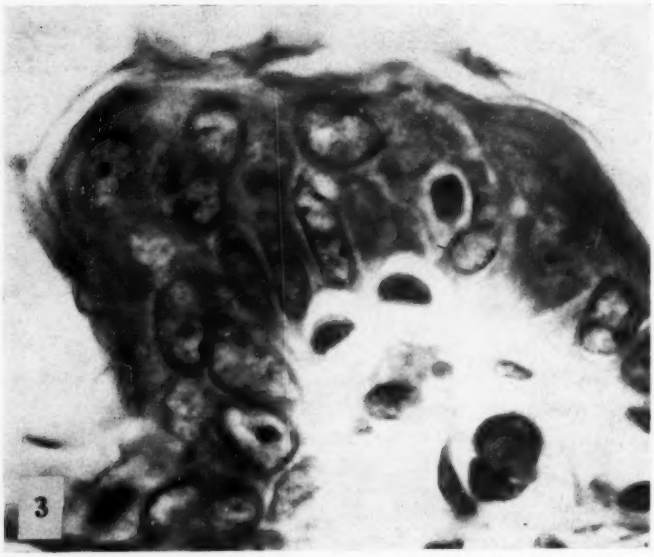


FIG. 1. Two clear cells (one in the center, one to the left) in the basal layer of the epidermis of a 21 day old male rat (number 690). The nuclei are similar in general staining property to those of the epithelial cells immediately above them but the cells are smaller and the cytoplasm almost completely lacks stain. X1822.

FIG. 2. Two lymphocytes with dense nuclei and one intermediate cell with a granular nucleus in the epidermis of a 600 day old male rat (number 910). Note the stratum granulosum in this older animal. X1822.



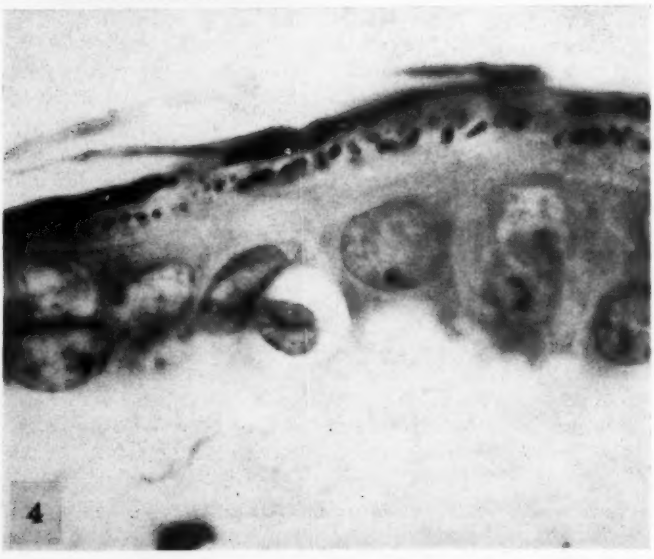
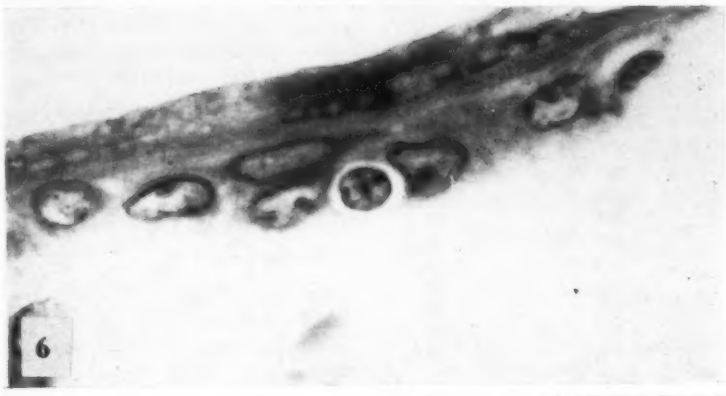


FIG. 3. A lymphocyte with dense nucleus entering the epidermis of a 300 day male rat (number 183). The nucleus of the lymphocyte is deformed by pressure of the wandering cell. To the left and below are two small cells apparently of mesodermal nature but just at the base of the epidermis. X1822.

FIG. 4. A clear cell in the epidermis of a 900 day female rat (number 991). The nucleus is very similar to that of nearby epithelial cells, although of smaller size. X1822.



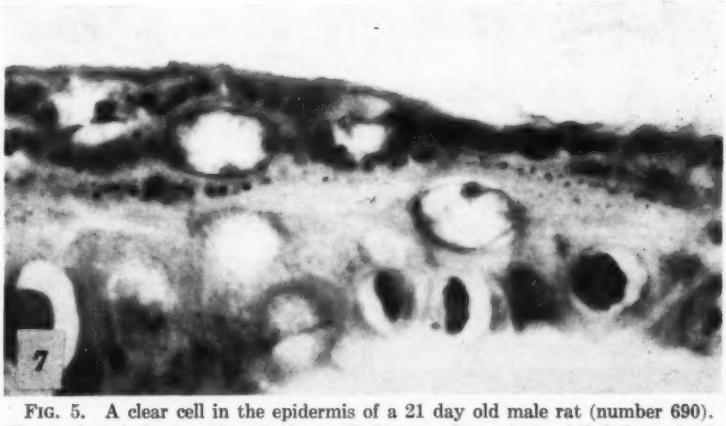


FIG. 5. A clear cell in the epidermis of a 21 day old male rat (number 690). The nucleus is large and vesicular, and the cytoplasm shows definitely stained portions. X1822.

FIG. 6. An intermediate cell in the epidermis of a 300 day old male rat (number 183). The nucleus is small and spheroidal but lacks the density of the nucleus of a lymphocyte.

FIG. 7. Mitotic figures in the epidermis of a 900 day female rat (number 991). At far right is a prophase and just to right of center a telophase. X1822.

present, namely, lymphocytes, intermediate cells, and clear cells. Counts of these types of cells (table 2) and statistical analysis of the results (table 3), in fact, show no significant differences in numbers of these cell types between the very young and the senile animals. It is true, however, that the range is greater from animal to animal in the older age group (table 3).

Discussion

The presence of usually motile cells such as the lymphocytes in the epidermis in animals at widely varying ages through almost the entire life-span of an animal raises the question of the interpretation of the morphologic picture observed. We may ask ourselves if there is a constant migration of these cells into the epidermis and a "using up," in some manner, of them after their entrance among the epithelial cells, or if the lymphocytes in the epidermis are static cells which have settled down and form a permanent part of this tissue? Is the epidermis, in fact, a type of lympho-epithelial structure, constantly composed of at least two very unlike types of cells?

Table 2. Older Middle-aged and Senile Rats
Data Obtained by Counts of 1,000 Cells Per Animal from Region of Back

Identification Number	Age in Days and Sex	Lympho-cytes	Intermediate Cells	Clear Cells	Total No. of Mitotic Figures
910	600 M	33	23	151	1
903	650 M	28	21	113	1
387	900 F	24	24	87	2
896	900 M	13	20	127	4
954	900 M	28	22	61	4
977	900 F	19	18	99	6
978	900 F	25	19	86	0
979	900 F	16	27	60	0
980	900 F	19	48	66	2
991	900 F	18	26	207	4
994	900 F	28	24	125	3
995	900 F	17	12	95	4
996	900 F	65	23	127	6

Table 3. Data on Lymphocytes, Intermediate Cells, and Clear Cells in Each of 3 Age Groups of Wistar Rats
The mean, with its probable error, and the range are given for each age group.

Age Group	Lymphocytes	Intermediate Cells	Clear Cells
21 day (9 animals)	23.7 ± 1.43	21.33 ± 1.54	89.33 ± 6.05
	13–38	11–29	61–157
300 day[1] (6 animals)	33.67 ± 2.55	6.3 ± 0.92	84.67 ± 2.90
	24–48	1–11	75–105
900 day (11 animals)	24.8 ± 2.72	23.91 ± 1.75	103.36 ± 7.20
	13–65	12–48	60–207

[1] See reference No. 6.

In attempting to decide which explanation carries greater weight, we naturally would consider, first, the condition in other types of epithelia in which lymphocytes have been described as occuring normally. These include the epithelia of the oesophagus, intestine, trachea and bronchi, vagina, uterus, oviduct, ureter, and bladder (18). In these locations the lymphocytes are generally accepted as migrant cells and indeed they frequently can be seen to be at different levels in the epithelium and in many cases, particularly in the intestine and the trachea, to pass completely through and enter the lumen. In the buccal cavity they appear to form the salivary corpuscles, which occur free in the saliva.

Thus, by inference, we would tend to interpret the presence of lymphocytes in the epidermis in young, middle-aged, and senile rats as indicating a constant migration of these cells and to believe that many generations of them take part in such migration.

A second argument in favor of a continuing entry into and turnover of lymphocytes in the epidermis arises from the very nature of this covering epithelium. It is a tissue which itself is undergoing a constant turnover, with the superficial layers desquamating and the cells of the deeper layers being renewed. It would seem a rather peculiar circumstance, to say the least, if the cells known to be motile and migratory, namely the lymphocytes, remained static in one position while the epithelial cells underwent this continuing change.

The question of the role of the lymphocytes in the epidermis is one not directly related to studies on aging as such but which has ramifications into many fields. If, as we believe for the reasons given above, there is a continuing migration of these cells into the epidermis, there must also be disposal of them there. Andreasen (1) believes that breakdown of lymphocytes does occur in the epidermis and that their products may be of importance to the proper epithelial cells of the layer.

We have studied lymphocytes in several locations in the body where a frank degeneration of these cells does occur (3, 4, 9). The process is a conspicuous one in the germinal or reaction centers in the spleen and lymph nodes in Wistar rats and consists in a pycnosis and karyorrhexis which we have described and pictured. No such process has been observed in the epidermis of the large number of animals which we have studied and hence, while some more subtle manner of degeneration may occur here, we do not have evidence of a breakdown of lymphocytes.

Our own hypothesis, of a transformation of these cells into the so-called clear cells and of these on into epidermal cells, meets with difficulties in relation to the germ-layer theory and also in regard to the dynamic interpretation of morphologic pictures. Nevertheless, it remains for us the most logical existing explanation of the occurrence of lymphocytes in normal epidermis.

Summary

A study has been made of the epidermis of 22 Wistar Institute rats of known age and consisting of young (21 days), and older middle-aged and senile animals (600-900 days).

Lymphocytes, intermediate cells, and clear cells are present in the epidermis in young animals (21 days) and in senile animals (900 days). Quantitative study and statistical analysis shows no significant difference in the relative numbers of these cell types at these widely different ages. Comparison with data obtained earlier on rats of 300 days shows the values to be similar here also.

The epidermis of rats of 600 to 900 days differs from that of rats of 21 to 300 days in showing a conspicuous stratum granulosum and a stratum corneum with closely adherent lamellae.

No evidence of degeneration of lymphocytes in the epidermis has been seen and the concept of transformation of these multipotential cells has received further support.

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CYTOLOGIC STUDIES OF THE SALIVARY GLANDS OF THE RAT IN REFERENCE TO THE AGING PROCESS

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CYTOLOGIC studies of the salivary glands in relation to the aging process have been carried out previously on human and animal tissues (2, 3, 11, 21). These studies, however, were limited to the nucleus and general cellular morphology.

Although the mitochondria and Golgi substance have not been investigated previously in the salivary glands of senile animals, numerous studies have been carried out on other tissues. Among cell types with comparatively short life-spans, Wiseman (23) observed a decrease in the number of mitochondria in circulating lymphocytes as the cells became older, and Cowdry (6) noted a diminished number of mitochondria in the more superficial, hence older epidermal cells of the stratum germinativum of the skin. Alterations of mitochondria and Golgi substance have been reported in the literature in cell types whose life-span is generally much longer than the above-mentioned types. Payne (18) observed in the senile fowl the formation of large vesicles from pre-existing mitochondria in cells of the pituitary and thyroid glands. Jayne (14) and Andrew and Kurtz (4), studying the rat adrenal and liver, respectively, reported similar vesicle formation in senile animals, but the forms were not as spectacular as those seen by Payne. Alterations in the Golgi substance were observed by Andrew (1) in the Purkinje cells of senile mice. He found that the typical reticular form seen in young animals gave way to one of granulation in senile animals. Stein, Caldwell, and Peters (20), also working with senile mice, reported that all of the cells of the anterior lobe of the pituitary except the basophiles contained much smaller Golgi networks than similar cells in young mice. Fragmentation of the Golgi substance was observed by Gatenby and Moussa (10) in sympathetic ganglion cells of old rabbits, and by Sulkin and Kuntz (22) in autonomic ganglion cells of senile dogs.

The present study deals with an analysis of possible morphologic alterations of the mitochondria and Golgi substance in the salivary glands of senile rats.

MATERIAL AND METHODS

The organs investigated in this work were the parotid and submandibular glands from 41 Wistar Institute rats. Of this group, 20 ranged in age from 100 to 300 days and were designated as young or adult. The remaining 21 animals were 620 to 997 days of age and were classified as senile, in view of the rapid increase in death rate during this period, the physical appearance of the animals, and the criteria applied by other investigators (2, 3). The animals had free access to food and water and were sacrificed in the mid-afternoon, at which time the rat ordinarily has been dormant for many hours. This was to insure minimum secretory activity in the salivary glands.

The organs were removed after anesthetizing the animals with pentobarbital-sodium and fixed in either a modified Champy's fluid (equal parts of 3 per cent potassium dichromate, 2 per cent osmic acid, and 1 per cent chromic acid) for 24 hours, or in Aoyama's formol-cadmium chloride mixture. The tissue fixed in Champy's fluid was washed for 24 hours, and half of this was post-osmicated in 2 per cent osmic acid for 5 days at 35-37 C. to impregnate the Golgi sub-

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[1] U. S. Public Health Fellow, National Cancer Institute, National Institutes of Health.

stance. The remainder of the tissue was sectioned and stained to demonstrate mitochondria by the Cowdry modification of Altmann's aniline-acid fuchsin stain. The tissue fixed with Aoyama's fluid was immersed or perfused. The perfusion equipment consisted of 2 flasks, one containing physiologic saline solution, the other, Aoyama's fluid. Each was suspended approximately 850 mm. above the animal in order to establish a hydrostatic pressure nearly equivalent to the mean arterial blood pressure of the rat. The flasks fed into a 3-way stopcock, to the outlet of which was attached a 20 gauge needle connected by means of a length of rubber tubing. The procedure was to expose the heart rapidly by bold dissection of the thoracic cage, insert the needle into the left ventricle, cut the right atrium or inferior vena cava, and start the flow of saline. After about 20 seconds, the fluid escaping from the cut was essentially free of blood and the stop-cock was turned to the fixing solution. When signs of fixation were evident, small pieces of tissue were excised and immersed in fixing fluid for the prescribed length of time. They were then silvered and reduced according to DaFano's method, sectioned, and gold toned before counter-staining with hematoxylin and eosin. Several specimens of fresh tissue were removed just prior to perfusion and fixed by immersion for comparison with the perfusion fixed material.

In the tissues fixed by immersion for demonstration of mitochondria, observations were made near the edges of the sections of minimize errors attributable to the slow penetration of fixative.

Results

Submandibular Gland

Mitochondria.—Observations were limited to the serous lobes of the submandibular gland, since the mucous portions of the gland react with the Champy's fluid and subsequent treatment in such a way as to obscure observations of the mitochondria.

In all of the young animals, the mitochondria in the serous cells of the submandibular glands were relatively thick rods and short filaments with smooth contours (fig. 1). They were quite numerous and evenly distributed throughout the cytoplasm. Their number, form, and distribution varied only slightly from cell to cell. In a few cells, elongated mitochondria were seen, but their contours were smooth, and the appearance of turgidity was evident. This uniformity in the over-all appearance of the section gave way to variations in the sections of tissues from the senile animals. In the latter, practically all of the mitochondria were tenuous and elongated, suggesting a diminution of mitochondrial material (fig. 2). Their number varied from cell to cell. The irregularity of contour suggested loss of rigidity or turgor in the mitochondria of many of these cells. The diameter of the shorter forms was also greatly reduced.

A peculiar cell type was observed occasionally in the glands from senile animals. Its features consisted of hypertrophied, irregular nuclei, cytoplasm, or both (fig. 3). This cell conformed to the so-called oncocyte, described previously by Hamperl (11) and Andrew (2, 3). The mitochondria in this cell type were seen to differ in no respect from those of the surrounding cells. In those oncocytes containing a larger number of mitochondria, the increase in number seemed to be proportional to the increase in cell volume.

Golgi Substance.—In the group of young animals the configuration of the Golgi substance varied little from cell to cell and from animal to animal (fig. 7). The general appearance was one of delicate strands located in the region between the cytoplasm and the compartment of secretion granules. The strands tended to follow the interface between cytoplasm and stored secretions, and in the Aoyama preparations where most of the secretion granules were dissolved out of the cells, it was seen that many delicate strands of Golgi material entered the storage compartment in trabecular-like strands of cytoplasm. In a few cells the strands tended

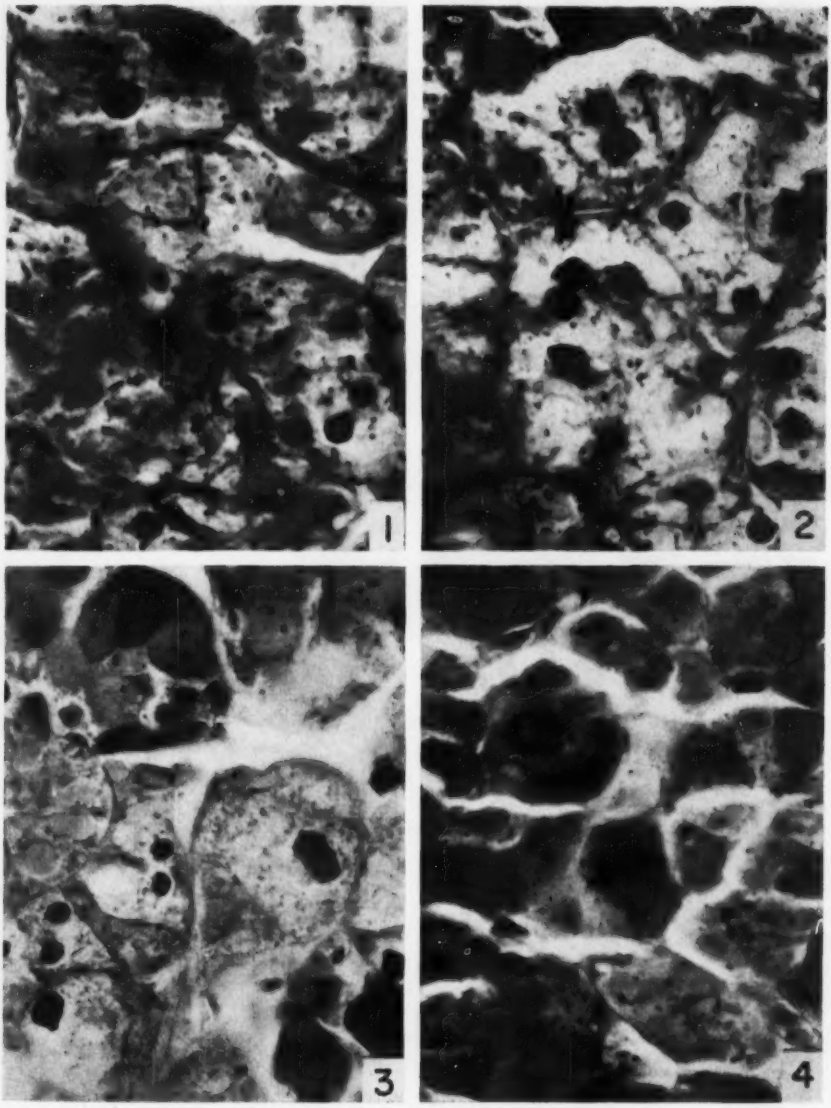

Fig. 1. 100-day old male rat, submandibular gland. The mitochondria are composed of thick rods and granules. They are evenly distributed within the cells, and their number from cell to cell is relatively constant. Champy fixation, acid fuchsin stain. 10X ocular; 90X objective.

Fig. 2. 900-day old male rat, submandibular gland. The thickness of the mitochondria is markedly decreased, and there are many long slender forms. The over-all effect is one of diminution of mitochondrial material. Champy fixation, acid fuchsin stain. 10X ocular; 90X objective.

Fig. 3. 887-day old male rat, submandibular gland. An oncocyte with hypertrophied nucleus can be seen. Note that the morphology of the mitochondria in this cell is similar to that of the surrounding cells. Champy fixation, acid fuchsin stain. 10X ocular; 90X objective.

Fig. 4. 100-day old male rat, parotid gland. The mitochondria are numerous and evenly distributed. They range in length from short spheroidal forms to elongated rods. The diameter of the spherical mitochondria is slightly variable. Champy fixation, acid fuchsin stain. 10X ocular; 90X objective.

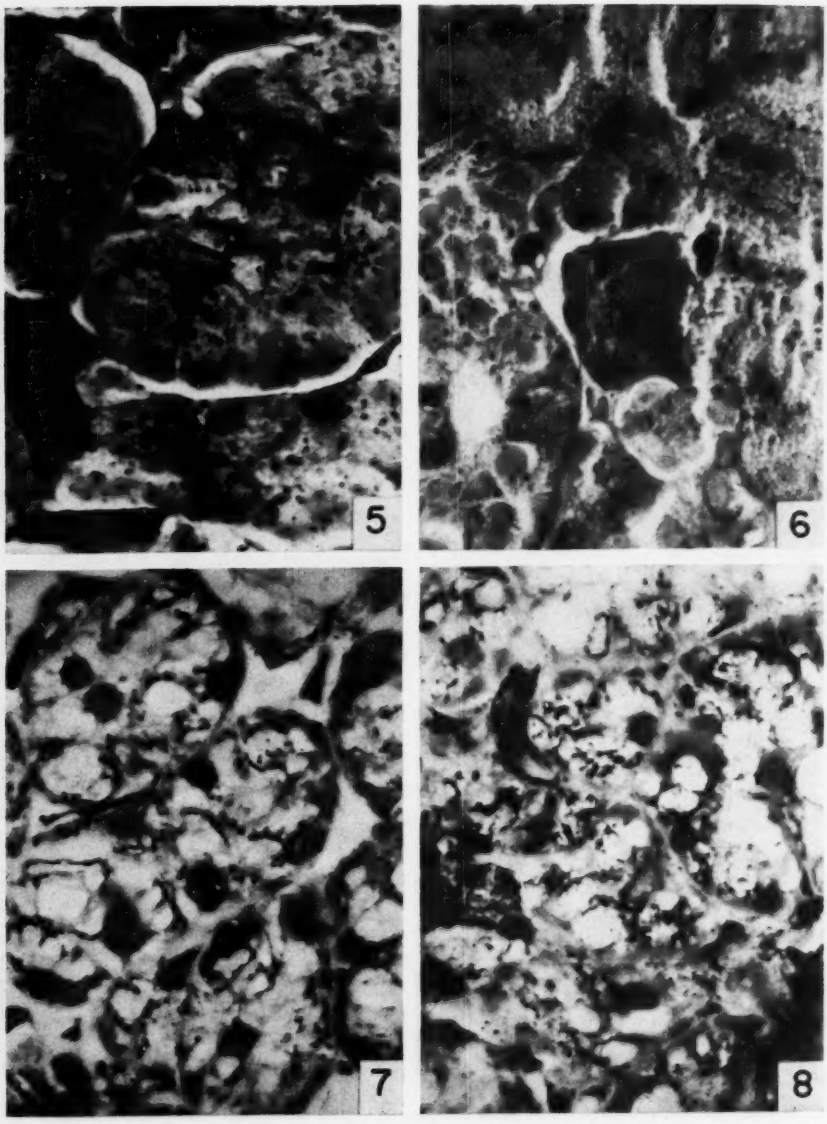

Fig. 5. 900-day old female rat, parotid gland. Variation in size and distribution of the mitochondria is pronounced, and only spherical mitochondria are visible. Champy fixation, acid fuchsin stain. 10X ocular; 90X objective.

Fig. 6. 997-day old male rat, parotid gland. Again, the uneven size and distribution of the mitochondria is evident, and many cells clearly show the distortion of the secretion granules. The peculiar dark multi-nucleated cell cannot be explained. Champy fixation, acid fuchsin stain. 10X ocular; 90X objective.

Fig. 7. 280-day old male rat, submandibular gland. The Golgi substance is composed of delicate strands which follow the interface between the cytoplasm and vacuoles which formerly housed the secretion granules. There is little variation in morphology from cell to cell. Aoyama preparation by perfusion. 10X ocular; 90X objective.

Fig. 8. 750-day old male rat, submandibular gland. Many cells contain a fragmented Golgi element. The strands, where intact, vary in thickness and quantity from cell to cell. Aoyama preparation by perfusion. 10X ocular; 90X objective.

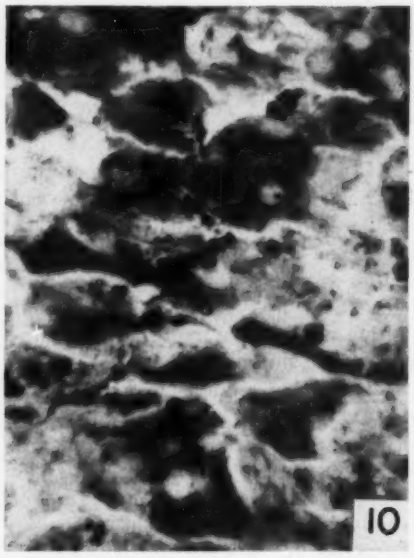

Fig. 9. 100-day old male rat, parotid gland. The Golgi element is composed of delicate strands and nets, usually apical to the nucleus. Some of the strands are spread out into the region of the secretion granules. Kolatchew-Nassonow preparation. 10X ocular; 90X objective.

Fig. 10. 885-day old male rat, parotid gland. The Golgi substance has contracted into tight, dense nets and clumps. The amount of Golgi material is variable from cell to cell and some evidence of fragmentation is visible. Kolatchew-Nassonow preparation. 10X ocular; 90X objective.

to be heavier, but still remained elongated.

In many cells of the submandibular glands in the senile group some fragmentation of formerly long strands of Golgi material into shorter, often thicker particles occurred (fig. 8). The variation in thickness of the strands from cell to cell was prominent in many cells. The amount of Golgi material was variable in different parts of the gland, and accumulation of dense osmiophilic droplets, noted only occasionally in the cells of young animals, was often pronounced in sections of tissues from the senile group. In some cells, these droplets were the only evidence of osmiophilic substance. The most extreme examples of fragmentation and variation in the Golgi substance from cell to cell were found usually in the oldest animals.

Parotid Gland

Mitochondria.—The morphology of the mitochondria in the cells of the parotid gland differed from that found in the submandibular gland. The typical cell in the parotid gland of the young rat contained rather thick mitochondria, and in most of the cells they were more numerous than in cells of the submandibular gland (fig. 4). The distribution was even, and their number seemed to be relatively constant from cell to cell. The shape varied from spheres to elongated filamentous forms; however, the variation in thickness was only slight. A few peculiar heavily staining cells were encountered whose mitochondria, in spite of poor contrast, could generally be discerned as a few dark spheres of material.

Observations of the parotid glands of senile animals disclosed that the mitochondria were not as evenly distributed as those in the younger animals, and the number varied

quite markedly, at times, from cell to cell (fig. 5). In the very old animals, a great variation in size and shape was noted, and a few very large mitochondria could be found in many cells. A large proportion were spherical in shape with widely variable diameters. It was noted too, that the secretion granules had lost their uniform spherical shape and were somewhat distorted (fig. 6). In many of the large spherical mitochondria the staining was less intense, suggesting that the enlargement was accomplished without the addition of stainable material. The appearance of the mitochondria found in the oncocytes of senile animals was similar to that of the surrounding cells.

Golgi Substance.—The Golgi substance in cells of the young parotid gland presented an appearance of relatively uniform strands or nets usually limited to a region just apical to the nucleus (fig. 9). Occasionally the strands extended out into the mass of secretion granules. The caliber of the strands was fairly constant, but variation in thickness was encountered in some of the cells.

In the senile animals, there was a tendency for the substance to be found in thicker, more closely knit strands (fig. 10). In addition, the older glands exhibited a lack of uniformity in the appearance of the network from cell to cell and fragmentation was encountered in many cells. Droplets were found in some cells of the senile glands and seemed to be similar to those encountered in the submandibular glands of senile animals.

Discussion

The observations revealed some interesting differences between young submandibular and parotid glands and senile submandibular and parotid glands. While the rod and club-shaped mitochondria observed in the serous portions of the submandibular glands from young rats were not far different from those seen in the parotid gland cells of the same age group, the morphologic alterations that developed with age in these 2 glands were divergent—the submandibular mitochondria developed into tenuous, often elongated forms, while the mitochondria of the parotid gland became spherical with age. The Golgi substance, too, exhibited this divergent behavior with age, but to a lesser extent than seen in the mitochondria. It is of interest that the cells studied in both of these glands were serous in nature, and it is likely that both are involved in the marked reduction in function known to occur in senility (15). Therefore, it would seem that no consistent morphologic alterations can be assigned to these cytoplasmic organelles as strict criteria of senility, even in closely related cell types.

Sulkin and Kuntz (22) in their studies of sympathetic ganglion cells from senile animals concluded that the altered morphology of the Golgi substance is a good indication of alteration in relative physiologic activity of the cell. Andrew (1), and Gatenby and Moussa (10) also have described extensive alterations of the Golgi substance in nervous tissue from senile animals. Although the changes in the appearance of this cytoplasmic component described in the present work could not be regarded as marked, the explanation may reside in the fact that the tissues studied here are fundamentally different from nerve cells in regard to relative age. Nerve cells fall into the class of "fixed post-mitotics" (6), i. e., the individual cells are about the same age as the adult animal, since no mitosis has occurred since shortly after birth. The salivary glands, on the other hand, are classified as "reversible post-mitotics," their cells retaining the ability to undergo mitosis throughout life. Although the rate of mitosis is low, mitotic figures have been observed in the salivary glands.

The lack of uniformity of the alterations in cells of tissues or organs from senile animals was first described by Cowdry (6), and was strikingly exhibited by Stein, Caldwell, and Peters (20), in their Golgi impregnations of the anterior lobe of the pituitary gland in mice. They found that the Golgi reticulum was decreased in size in acidophilic cells of senile animals, while that of the basophiles remained unchanged.

The perfusion studies, although carried out

on a limited scale, were successful in demonstrating that the classical configuration of the Golgi substance was not caused by slow, differential penetration of the fixing fluid as claimed by Palade and Claude (16, 17). Dalton (7) fixed liver and intestinal epithelium of mice by perfusion with Champy's fluid and found the typical arrangement of the Golgi element after post-osmication. These results, after relatively instant fixation, along with those of Simpson (19), who described the typical picture in intestinal mucosa after freeze-drying the tissues, and Dalton and Felix (8), who described the Golgi apparatus in living mouse epididymis and intestinal epithelium, would seem to leave little doubt that the reticular shape of this cytoplasmic structure is the form in the living cell and that its structure is not an artifact of fixation.

The alteration of the size, shape, and distribution of the mitochondria in the senile cells investigated can best be accounted for by assuming fundamental physiologic changes both extrinsic and intrinsic to these cytoplasmic organelles. The work of Honda (13), Hirsch (12), Duthie (9), and Claude (5) established persuasive evidence that the mitochondria are intimately associated with the formation of zymogen in exocrine cells. These data, in addition to the studies by Meyer and associates (15) in which the ptyalin content of saliva from senile individuals was found to be reduced to one-fourth of that found in young individuals would seem to relate a good portion of the changes described in this work to intrinsic alteration of mitochondrial physiology. The marked variation from cell to cell in the arrangement of the mitochondria and Golgi substance suggests a loss of unified response to the metabolic regulating mechanisms of the body, and by this loss of unity in function the resulting decrease in total efficiency of the salivary glands could account in part for the decreased enzyme content in the saliva of senile individuals.

Summary

1. Alterations related to age were observed in the morphology of the mitochondria and Golgi substance in cells of the submandibular and parotid glands.

2. The mitochondria in the submandibular gland changed from evenly distributed plump rods in the young rat to tenuous, irregularly dispersed forms in the senile animal, with an apparent decrease in mitochondrial substance. In the parotid gland cells of young rats, the mitochondria were evenly distributed, numerous small rods and spheres, while the cells from the senile animals contained almost entirely spherical mitochondria, with great variation in number and size from cell to cell.

3. The Golgi substance in the submandibular gland cells of the young rat was found to be in the form of delicate strands, with little variation from cell to cell, while the same organs in senile animals presented areas in which uniformity of thickness and integrity of strands were lacking. Heavily blackened droplets were evident in osmium preparations. Differences in the appearance of the Golgi element between young and old parotid glands tended to be subtle. Along with loss of uniformity, there was a tendency for the networks to be contracted and closely knit in the senile animals. Again, dark staining droplets were evident in the osmium preparations.

4. Successful preparations of "typical" Golgi networks after perfusion fixation lend additional evidence to the belief that this cytoplasmic component is not artifically produced by slow diffusion and penetration of certain fixing fluids.

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ACTH ADMINISTRATION, ADRENAL RESPONSE, AND AGE

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(From De Gamles By, Copenhagen, Denmark)

A NUMBER of the physiologic and pathologic phenomena considered characteristic of old age have been attributed to changes in the anterior part of the pituitary gland and the adrenal cortex. The production of various highly purified adrenocorticotropic hormones has rendered it possible to investigate more exactly the functions of the pituitary and adrenal glands and their relation to old age.

Thus Solomon and Shock (20) have investigated whether there was any difference in the response of the adrenal cortex in elderly and young persons to the administration of a single dose of ACTH. Duncan and associates (9) have carried out similar supplementary experiments.

It has also been the purpose of the present study to investigate the response of normal aged persons to ACTH and to compare the reactions of elderly and young persons to the administration of this hormone.

MATERIAL AND METHODS

Six subjects (4 men and 2 women) between 64 and 89 years of age were chosen for the investigation. The subjects were inmates of De Gamles By in Copenhagen, a municipal institution for old individuals, and were in a fairly good general state of health. For the purpose of comparison, 4 women between 33 and 39 years of age were similarly examined. These persons were also in good physical condition both before and during the experiments, except that one subject, E.O., 39 years, developed pre-tetanic symptoms following ACTH administration. Individual data concerning the 10 subjects are shown in table 1.

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The 6 elderly subjects received a fairly uniform diet. Two of the 4 young persons were convalescent patients in the hospital unit of the institution and both received the usual ward diet. The 2 other individuals were ambulatory and received ordinary food.

The subjects were first studied during a five day control period. On the following two days 10 I.U. of ACTH[1] were given intramuscularly every six hours, a total of 80 I.U. being administered during the 48 hour period. The observations on the individuals were subsequently continued during a two day recovery period.

The following examinations were made *daily* in each of the 10 subjects: measurement of temperature, pulse rate, blood pressure, diuresis, and determination of the 24-hour urinary excretion of 17-ketosteroids (6) and reducing corticoids (21).

In addition, a series of laboratory tests were carried out once during the control period and seven and sixty hours after the last injection of ACTH. These tests included sedimentation rate (24), total leukocyte, eosinophil, and erythrocyte counts; serum calcium (23), blood sugar (14), and serum cholesterol (19). Estimations were further made of the content in the urine of uric acid (2), creatinine (12), and cholesterol (5). It should be noted that none of these analyses were performed during the actual period of ACTH administration; the time of seven hours after the injection of the last dose of ACTH was deliberately chosen in order to gain an impression of the cumulative effect of the administration of 80 units of the hormone.

In the present study it was not possible to carry out determinations of the content of potassium in the blood. In order to obtain

[1] The Danish preparation "Acton," batch No. 5105.

TABLE 1. DATA ON SUBJECTS

Name	Age (Years)	Sex	Height (Cm.)	Weight (Kg.)	Occupation	Remarks
A. J.	33	F	155	62	Nurse	Chronic colitis*
E. T.	35	F	170	102	Nurse	Obesity. Diagnosis of Cushing's syndrome considered but not verified
G. H.	37	F	160	63	Nurse	Convalescent following infectious hepatitis*
E. O.	39	F	158	61	Nurse	No disease condition
S. A.	64	M	168	59	Former bricklayer	Chronic bronchitis; pulmonary emphysema
A. S.	67	F	139	49	Former housewife	Osteomalacia; previous gastric resection
E. P.	72	M	163	69	Former stonemason	Chronic cholecystitis
J. N.	74	M	174	75	Former bricklayer	Arteriosclerosis; previous right supracondylar amputation
C. E.	83	M	171	51	Former foreman	Auricular fibrillation; prostatic hypertrophy
C B.	89	F	152	72	Former housewife	Rheumatoid arthritis

* These patients were examined immediately prior to discharge from hospital.

an indication of possible electrolyte changes during ACTH administration, electrocardiograms were recorded on all the 10 subjects during and after hormone treatment.

RESULTS

Clinical Observations

All 6 elderly and 2 of the young subjects felt completely well during the period of ACTH administration. No physical changes were observed, but such could hardly be expected with the relatively small amount of hormone given.

The 39 year old woman, E. O., complained of headache and nausea and stated that she felt quite ill. In this individual pre-tetanic symptoms developed in connection with a marked reduction of the serum calcium concentration. All the symptoms disappeared twenty-four hours after the last ACTH administration.

The 35 year old woman, E. T., developed catarrh with cough, coryza, and subfebrile temperature twenty-four hours after receiving the first dose of ACTH. Her condition improved in the course of about four days and she was able to continue working throughout the whole period.

There were no changes in pulse rate, temperature, or blood pressure during the study period, and none of the subjects developed edema.

Laboratory Findings

The results of the laboratory tests are shown in tables 2 and 3.

Sedimentation Rate.—The sedimentation rate rose to values between 23 and 44 mm. per hour in 4 of the elderly subjects and remained unchanged in 2 of the same group. There was no effect on the sedimentation rate in 3 of the young subjects. A rise occurred in the fourth, E. T., but, as mentioned previously, this person developed catarrh and became sub-febrile during the study period.

Number of Eosinophil Leukocytes in the Blood.—A decrease in the number of eosinophils of about 50 to 90 per cent occurred during ACTH administration in all 10 persons examined. In 4 of the elderly subjects the number of eosinophil cells fell to less than 25 per cent of the value during the con-

TABLE 2. DATA ON URINARY EXCRETION PER 24 HOURS OF 17-KETOSTEROIDS AND REDUCING CORTICOIDS BEFORE, DURING, AND AFTER ADMINISTRATION OF ACTH TO 4 YOUNG AND 6 ELDERLY SUBJECTS.

Investigation period	Day	A.J. 33 F.			E.T. 35 F.			G.H. 37 F.			E.O. 39 F.			S.A. 64 M.			A.S. 67 F.			E.P. 72 M.			J.N. 74 M.			C.E. 83 M.*			C.B. 89 F.		
		17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.	17-ketosteroid per 24 hrs.	Corticoid per 24 hrs.	Urine per 24 hrs.
		mg.	mg.	ml.	mg.	mg.	ml.	mg.	mg.	ml.	mg.	mg.	ml.	mg.	mg.	ml.	mg.	mg.	ml.	mg.	mg.	ml.	mg.	mg.	ml.	mg.	mg.	ml.	mg.	mg.	ml.
Control	1	4.5	0.32	1250	13.6	0.70	940	6.0	0.19	800	9.0	1.32	1550	5.4	1.00	1300	2.0	0.75	950	3.2	0.45	1210	3.2	0.76	410	3.2	1.12	860	2.2	0.51	1050
	2	6.2	0.46	980	15.2	0.75	1050	5.0	0.55	800	9.3	1.19	1280	5.2	0.75	780	2.7	0.55	750	4.1	0.50	1300	4.8	0.75	625	2.8	1.04	920	1.8	0.60	1000
	3	4.6	0.36	650	17.2	0.80	1100	3.4	0.52	650	10.5	0.96	1475	7.1	0.72	1250	2.6	0.35	925	3.8	0.26	1350	5.4	0.60	650	5.0	1.10	820	2.1	0.25	1000
	4	8.9	0.81	980	16.5	0.76	1100	3.5	0.89	850	9.5	1.19	1150	6.5	0.99	1210	2.5	0.48	975	3.8	0.40	935	4.6	0.90	645	7.5	1.62	670	2.2	0.60	1100
	5	5.1	0.44	820	15.6	0.76	1150	5.3	0.81	1200	10.5	0.85	825	5.2	0.85	1150	1.3	0.46	1000	3.7	0.45	685	3.4	0.75	765	8.1	1.62	620	2.0	0.30	1200
ACTH	6	4.1	0.94	900	13.1	0.78	1400	7.6	1.62	980	12.8	1.20	950	7.6	1.90	750	5.1	1.20	550	3.7	0.70	900	5.4	0.80	630	5.4	0.70**	600	2.8	1.45	1025
	7	4.2	0.60	375	17.0	1.33	1280	9.0	1.46	700	15.2	1.50	725	13.6	2 80	520	5.2	2.10	925	4.8	0.80	1030	3.8	1.25	510	5.6	1.72	580	2.4	0.55	725
Recovery	8	3.8	0.48	480	14.4	0.66	850	6.1	0.54	680	7.6	1.25	800	7.8	1.45	805	5.5	0.80	1625	2.5	0.65	715	7.2	2.50	430	3.1	1.10	1200	2.4	0.50	2475
	9	9.6	0.96	1200	18.0	1.33	1050	5.4	1.07	1200	7.4	1.15	1100	8.4	1.10	1025	4.8	0.70	1450	2.6	0.60	1110	6.3	0.60	540	2.5	1.02	1120	2.0	0.52	1775

* This person received 40 I.U. ACTH daily on the 4th, 5th, 6th, and 7th day.
** The value is presumably the result of a technical error.

TABLE 3. HEMATOLOGIC, METABOLIC, AND ELECTROCARDIOGRAPHIC DATA ON 4 YOUNG AND 6 ELDERLY SUBJECTS BEFORE, DURING,* AND AFTER ACTH ADMINISTRATION.

Name, Sex, and Age	Relation to ACTH Administration	Erythrocyte Sedimentation Rate mm./hour	Erythrocytes mill. per cu. mm.	Leucocytes per cu. mm.	Eosinophils per cu. mm.	Serum Calcium mg.%	Blood Sugar mg.%	Serum Cholesterol mg.%	Urine per 24 hours ml.	Uric Acid in Urine mg. per 24 hours	Creatinine in Urine mg. per 24 hours	Uric Acid/Creatinine Ratio	Urinary Cholesterol mg. per 24 hours	Some Electrocardiographic Measurements		
														Breadth of T_1 Wave sec. × 0.01	Height of T_1 Wave mm.	Length of Q-T_1 Interval sec. × 0.01
A.J. F. 33	before	6	4.61	4560	244	10.6	102	231	1250	375	1100	0.35	2.00	5	3	11
	during*	8	4.83	5040	120	8.2	83	263	375	244	600	0.40	1.56	5	2	9
	after	5	4.97	5400	150	10.3	124	241	1200	720	1080	0.69	2.95	6	3	11
E.T. F. 35	before	15	4.27	5800	400	9.5	127	199	940	458	1550	0.30	1.61	6	2	11
	during*	32	3.94	6280	160	7.3	89	179	1280	448	1600	0.28	1.54	6	2	10
	after	30	4.07	7720	194	8.9	108	215	1050	1008	1773	0.58	1.64	6	2	11
G.H. F. 37	before	13	3.95	4840	194	11.1	98	225	850	213	1012	0.21	0.98	7	2	11
	during*	13	3.72	8960	25	8.5	113	213	700	385	1060	0.36	2.17	7	2	11
	after	11	4.68	6200	394	9.4	99	187	1200	420	1140	0.37	2.28	7	3	9
E.O. F. 39	before	3	4.37	6720	231	9.6	92	196	1550	405	1200	0.33	0.31	7	3	9
	during*	6	4.51	7760	119	6.5	85	162	950	408	1093	0.38	0.55	5	3	9
	after	4	4.13	8280	294	8.3	88	171	800	680	1009	0.67	0.64	6	2	9
S.A. M. 64	before	13	3.72	5280	194	11.0	79	169	780	431	858	0.50	0.60	5	2	11
	during*	32	3.61	8320	6	11.3	194	172	520	291	558	0.52	0.34	7	1	11
	after	7	4.10	7000	144	10.3	86	137	1025	595	1332	0.47	1.33	6	2	11
A.S. F. 67	before	6	5.65	7000	125	10.4	83	285	750	348	570	0.60	0.45	7	3	13
	during*	44	4.85	7400	13	9.4	119	252	925	481	674	0.84	0.79	7	3	13
	after	12	4.17	5800	75	10.8	83	236	1450	290	681	0.43	0.51	6	2	11
E.P. M. 72	before	10	4.30	5820	288	9.6	83	187	1300	520	1079	0.50	0.53	8	3	12
	during*	6	4.19	6760	113	9.9	81	179	1030	474	797	0.59	0.93	8	3	12
	after	4	4.01	7660	94	9.8	78	178	1110	488	710	0.69	0.64	6	3	12
J.N. M. 74	before	9	5.04	4720	506	11.1	85	231	625	388	1044	0.37	0.50	6	3	11
	during*	6	5.04	8360	25	11.0	88	238	510	388	246	1.58	0.75	6	1	12
	after	7	4.44	7240	494	10.1	79	206	540	292	912	0.32	0.48	6	2	10
C.E. M. 83	before	11	4.28	5320	19	8.9	101	96	860	387	937	0.40	13.10	. .	. .	. .
	during*	36	3.95	6800	6	9.0	122	123	620	520	217	2.40	18.10	. .	. .	. .
	after	19	4.30	5950	38	11.4	82	123	1120	825	392	2.10	10.30	. .	. .	. .
C.B. F. 80	before	13	3.21	5200	188	11.7	68	279	1060	380	530	0.70	0.98	7	2	11
	during*	23	2.87	6640	38	10.8	137	283	725	479	225	1.93	1.16	7	2	11
	after	20	3.34	6840	113	11.0	96	268	1775	497	710	0.70	1.08	7	2	11

* These observations were made seven hours *after* the last injection of ACTH.

trol periods. This was the case in only 1 of the young persons (table 3).

Number of Neutrophil Leukocytes in the Blood.—In the present study (table 3) slight neutrophilia was found during ACTH administration, but no definite change was noted in the number of erythrocytes. There was no difference between the response of the young and the old subjects.

Serum Calcium.—The serum calcium was scarcely affected during ACTH administration in the 6 elderly subjects, but there was a marked decrease in all 4 young persons.

Blood Sugar.—The blood sugar increased during ACTH administration in 4 of the elderly and very slightly in 1 of the young subjects. There was no alteration in sugar concentration in the other 2 elderly and 1 of the young persons. A decrease of blood sugar concentration occurred in the other 2 young persons.

Serum Cholesterol.—As will be seen from table 3, no regular change occurred in the serum cholesterol values during ACTH administration. Subject C. E., aged 83 years, showed unusually low figures, particularly in the control period (96 mg.%). The 24-hour excretion of cholesterol in the urine also seemed to be independent of ACTH administration. Subject C. E. (83 years) had an unusually high urinary cholesterol content, and this increased during the administration of ACTH.

Diuresis.—This is generally stated to vary regularly during ACTH administration, partly as a result of primary sodium retention and secondary potassium excretion, i.e., first a decrease followed by an increase of diuresis. However, in the present study there was no marked change of this character in the diuresis.

Urinary Excretion of 17-Ketosteroids.—Administration of ACTH caused essentially the same increase in 17-ketosteroid excretion in the old and the young subjects. Thus the excretion increased in 3 of the elderly and 2 of the young subjects. The 3 other elderly persons showed no increase. In the 33 year old woman, A. J., the 17-ketosteroid excretion decreased during ACTH administration. In the 35 year old person, E. T., there was no change in the ketosteroid excretion, which was abnormally high both before, during, and after ACTH administration.

Urinary Excretion of Reducing Corticoids.—The excretion of corticoids increased to a varying extent in all 10 subjects. In 3 of the young and 3 of the old individuals the rise valued less than 100 per cent. The increase in corticoid excretion was on the average relatively greater in the elderly (116 per cent) than in the young subjects (69 per cent). There was no consistent relation between the excretion of 17-ketosteroids and corticoids.

Urinary Excretion of Uric Acid.—The 24-hour uric acid excretion in the urine increased to varying extents during the ACTH administration or in the recovery period in 4 of the elderly and all of the young subjects. In 2 of the elderly individuals the uric acid content was not influenced by ACTH administration (table 3).

Urinary Excretion of Creatinine.—A distinct fall in the urinary creatinine content was observed in 5 of the elderly subjects. In 4 of these, this fall was followed by a compensatory rise during the recovery period. Only in 1 of the young persons was there a decrease in the amount of urinary creatinine during the administration of ACTH (table 3). On the basis of the concentration of these two substances in the urine before, during, and after ACTH administration, the uric acid-creatinine ratio has been calculated, as shown in table 3. This ratio increased during ACTH administration to varying extents in all the elderly persons but only slightly in the young subjects.

Electrocardiography.—No changes were observed in the electrocardiograms suggestive of hypopotassemia or hypocalcemia.

Comparison Between Response to ACTH Administration in Young and Elderly Subjects

The results of the various laboratory

analyses reported above indicate that the response of the young and elderly subjects to ACTH administration seems to vary with regard to sedimentation rate, eosinopenia, serum calcium, blood sugar concentration, corticoid excretion, and the uric acid-creatinine ratio. The general directions of the observed changes are listed in table 4.

TABLE 4. COMPARISON OF CHANGES IN RESULTS OF SOME LABORATORY TESTS FOLLOWING ACTH ADMINISTRATION TO YOUNG AND TO OLD INDIVIDUALS.

Laboratory Test	Young Subjects	Old Subjects
Sedimentation rate	No change	Increase
Eosinophils	Decrease	Marked decrease
Serum calcium	Decrease	No change
Blood sugar	No change	Increase
Urinary 17-ketosteroids	Increase	Increase
Urinary corticoids	Increase	Greater increase
Urinary creatinine	No change	Decrease
Uric acid/creatinine ratio	No change	Increase

For the purpose of quantitative comparison the changes in some of these values following ACTH administration in the young and old individuals are presented graphically in figure 1. The figure in addition contains observations with respect to the excretion of 17-ketosteroids. In this figure the pre-ACTH values or their averages have been taken to be 100 per cent and the alteration of these values during ACTH administration (expressed as percentages) has been calculated on the basis thereof. As will be seen from tables 2 and 3 all the pre-ACTH values in these 7 examinations were within the normal range, with the exception of the number of eosinophils in the blood of the 83 year old man, C. E., in whom a condition of eosinopenia was found.

The sedimentation rate and blood sugar concentration showed a tendency to increase in the old subjects but not in the young. The eosinopenia was more marked in the old than in the young persons, whereas a decrease in the serum calcium concentration occurred only in the young, but not in the elderly individuals.

DISCUSSION

In this study all 10 subjects responded to 80 I.U. ACTH administered in the course of 48 hours. The responses were not uniform, neither within the group of elderly nor within the group of young subjects. However, the method of response seemed to differ in certain characteristic ways in the aged and in young persons. Nevertheless it should be emphasized that the conclusions presented here must be evaluated with reserve on account of the relatively few subjects examined.

Temperature, pulse, and blood pressure did not alter in any of the 10 subjects as a result of ACTH administration. This was to be expected, considering the fact that the doses of ACTH were small and a purified vasopressin-free ACTH preparation was used. Using higher doses, various workers, including Jailer (16), Brust and associates (4), have found somewhat higher pulse frequency and a slight rise in blood pressure.

The response of the sedimentation rate to the administration of ACTH seems to be dependent on age, an increase being found in the old persons but not in the young subjects. It seems to be generally agreed that the sedimentation rate and the content of fibrinogen in blood are correlated. Fearnley and Bunim (10) examined the effect of a single, relatively small dose of ACTH on the sedimentation rate and plasma fibrinogen in 7 persons between 20 and 30 years of age. They found a drop in the concentration of plasma fibrinogen in 4 cases, a rise in 2 cases, and no change in 1 case.

The difference between the state of the sedimentation rate after ACTH administration in elderly and young subjects in the present study cannot be explained. It is possible that ACTH administration causes the organism to regulate its plasma fibrinogen content in such a way that an increase takes place if the original amount is low and a de-

FIG. 1.

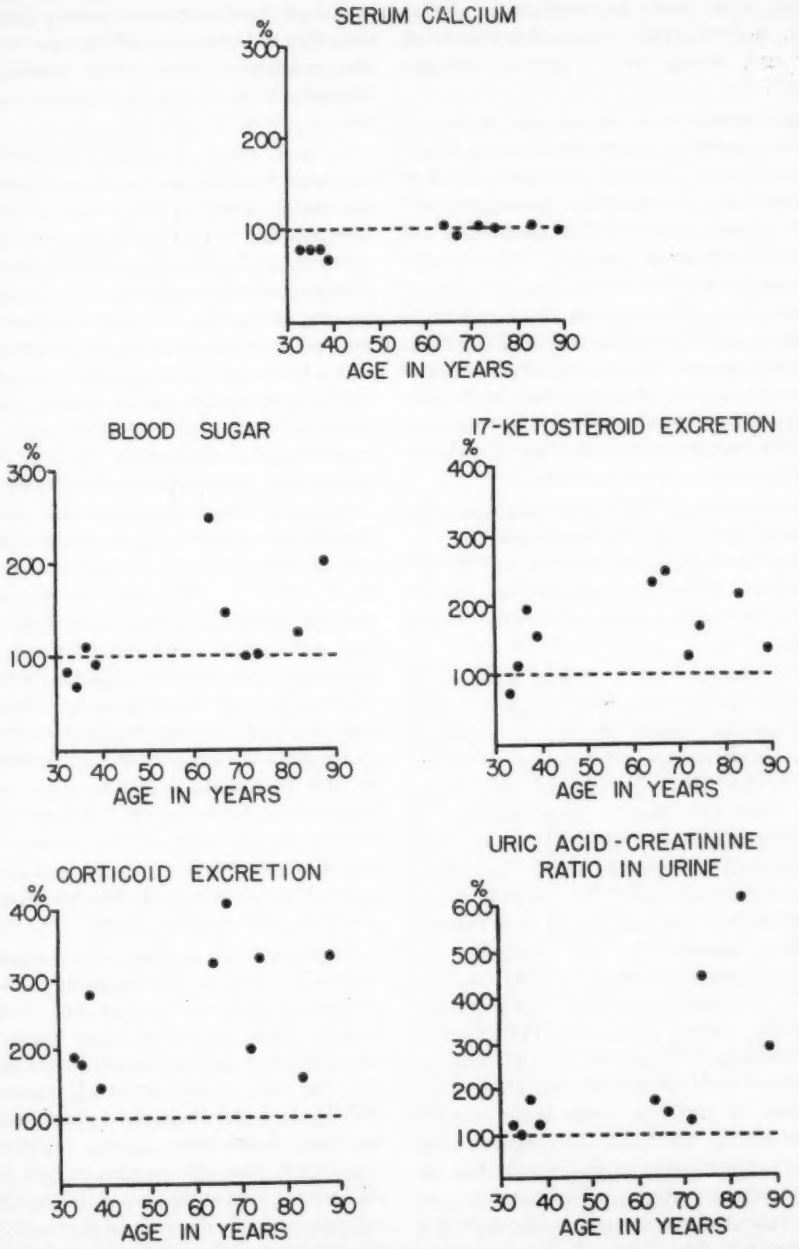

FIG. 1. Scatter plots of various ACTH responses against age. The data represent per cent deviations from pre-ACTH values occurring during ACTH administration. The 100 per cent level indicated in the figures by dotted lines represents the average of values observed before hormone administration.

crease if the original amount is high. However, this alone would not explain the difference in sedimentation rate alterations in elderly and young normal persons treated with ACTH.

Several writers have stated that the number of neutrophils and erythrocytes in blood shows consistent changes following ACTH administration. Palmer and associates (18) found in experiments with rats that a marked neutrophilia occurred after ACTH administration and also after adrenalectomy. Finch and associates (11) reported the same findings after administration of ACTH to a number of patients with rheumatic affections. These same authors observed that in anemic patients the number of erythrocytes rose during ACTH administration but remained unchanged in non-anemic persons.

As in all other ACTH investigations (13), eosinopenia was also demonstrated in the present study in conjunction with ACTH administration. The response in the elderly seemed to be more marked than in the young subjects.

It is of interest that a definite decrease in serum calcium was observed in the 4 young persons as the result of ACTH administration. Such decrease did not occur in the elderly individuals. In one of the young persons there was such a large decrease in serum calcium content that pre-tetanic symptoms occurred. However, this did not affect the electrocardiogram. The present study does not permit the drawing of any definite conclusions concerning the apparent instability of serum calcium concentration during ACTH administration to young people. Perhaps the reason is that ACTH causes a greater excretion of calcium in the urine in both elderly and young, but the elderly are better able to mobilize their bone calcium than the young, and thus the concentration in serum is maintained in the elderly but decreases in young persons. The fact that calcium excretion increases as a result of ACTH administration has been shown by other workers, who do not seem to have emphasized that the calcium level in blood after ACTH administration would appear to be more stable in elderly than in young persons and that this difference is perhaps due to the fact that calcium is more easily mobilized from the bone tissue in elderly than in young people.

As mentioned previously, a tendency to increased blood sugar values was observed in the elderly subjects following ACTH injection. It has been stated by a number of investigators (7, 16) that ACTH increases the gluconeogenesis and acts as "anti-insulin." On the other hand, other workers do not seem to have demonstrated any difference between the response of the blood sugar during ACTH administration in elderly and young persons. As mentioned previously, the few examinations comprising this material do not permit conclusions to be drawn. However, it can be assumed that the increases in blood sugar observed in 3 of the elderly persons and the lack of any appreciable increase in the other 3 elderly and the 4 young subjects could be explained by the fact that the increased gluconeogenesis caused a compensatory rise in the insulin production. Where, because of sclerosis or other pathologic changes, the pancreas has not maintained its normal function, the gland would not be able to maintain the normal sugar concentration of the blood. However, where the function is more or less intact, a lesser rise or no rise will be seen, as the case may be, or in the event of an over-compensation, possibly a fall may be found.

A number of authors have described a marked decrease in the serum cholesterol content in conjunction with ACTH administration. The fact that this could not be demonstrated in the present study is chiefly due to the relatively small amounts of ACTH used and the short control period. It has been shown from Conn's experiment (8) and others that the maximum fall in serum cholesterol concentration could not be demonstrated until about 5 to 8 days after administration of 70 to 100 mg. of ACTH daily.

Several investigators (17, 21) have reported that excretion of 17-ketosteroids and reduc-

ing corticoids in the urine decreases with age. It has further been demonstrated that administration of ACTH causes an increased excretion in the urine of the steroids mentioned and that the excretion of corticoids increases proportionally more than the excretion of 17-ketosteroids.

It has been possible to confirm these findings in the present study. Only 3 of the elderly subjects responded to ACTH with increased excretion of 17-ketosteroids. Yet this was not an indication of a general reduction of adreno-cortical function with age since the other 3 elderly subjects who showed no increase of excretion of 17-ketosteroids had a marked increase in their corticoid excretion; in fact, 2 showed a considerable rise (C. B. and J. N.). This might indicate that the production of 17-ketosteroids and reducing corticoids takes place in different sections of the adrenal cortex, but it cannot be excluded that a renal effect might be of significance here.

Subject E. T. had quite a high excretion of 17-ketosteroids which was not affected by ACTH administration. However, excretion of corticoids was within normal limits and was affected to a certain degree by administration of ACTH. This would support the hypothesis that 17-ketosteroids and corticoids are produced in different sections of the adrenal cortex and would weaken the assumption that the difference between excretion of 17-ketosteroids and corticoids is dependent on the function of the kidneys.

The urinary uric acid and creatinine excreted in conjunction with ACTH administration have been studied by many workers. Among others, Duncan and associates (9) and Ingbar and associates (15) have shown that the excretion of urinary uric acid increases somewhat during ACTH administration. These authors found the excretion to be the same in elderly and young subjects, whereas Solomon and Shock (20) found less uric acid excretion in elderly than in young subjects treated with ACTH. In the present study neither increased uric acid excretion nor correlation between excretion and age could be found. There was perhaps a tendency to somewhat higher excretion during or after ACTH administration in the 4 young subjects.

On the other hand, the creatinine excretion seemed to be dependent on ACTH administration, and this relation appeared to be mainly within the group of elderly persons. The apparently inconstant creatinine excretion caused by ACTH is somewhat surprising, since the majority of authors who have investigated similar problems have stated that the creatinine excretion is fairly constant and independent of ACTH administration (1, 22). Repeated control analyses made at the writer's and at another laboratory showed identical results, and thus it seems to be confirmed that the excretion of urinary creatinine can vary with administration of ACTH, particularly in elderly persons. Both Taussky and associates (22) and Solomon and Shock (20) have shown that the relation between the amounts of urinary uric acid and creatinine (U/Cr.) rises during and after administration of ACTH. The latter authors found, as did the writer, that there was a decrease in urinary creatinine during ACTH administration to elderly individuals.

Research concerning urinary cholesterol is rarely mentioned in the literature. The amounts of cholesterol excreted are only minimal and in the present study amounts lying between 0.3 mg. and 3 mg. per 24 hours were generally found. The figures were perhaps slightly higher in younger than in elderly subjects. In one case, an 83 year old man, relatively high urinary cholesterol values were found, 10 to 18 mg. There was no correlation between blood and urinary cholesterol found and the ACTH administered.

Summary

Results of a comparative study of the response to administration of ACTH during a short period to 6 elderly and 4 young subjects are presented. Several hematologic, metabolic (including hormonal), and other changes in these persons before, during, and

after ACTH administration were observed.

It would seem from this study that adreno-cortical response to ACTH administration is equally great in elderly and young persons, although there is some indication that old and young individuals respond in qualitatively different ways.

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THE RETENTION OF CALCIUM FROM GYPSUM AND PHYTIN BY THE ALBINO RAT IN RELATION TO LIFE SPAN*

PART I.

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THE importance of studying the utilization of calcium salts in the animal diet has long been recognized. The problem of osteomalacia is not restricted to the peoples of Asia, there being much evidence that in the Western World such deficiencies are frequently present (6). Thus, in borderline cases, the assimilability and consequently the comparative value of different calcium compounds for bone building become important; further, as the organism ages, the problem assumes an even greater significance, for the decreased efficiency of the body with respect to calcium utilization has also to be considered. Before a recommendation for a source of calcium is made, it is necessary that it not only be obtainable in large amounts and inexpensively but also that it must be available to the organism at all ages to an appreciable extent.

The two salts chosen as the subject of the present investigation were calcium sulphate and phytate, which are fairly well represented the world over, the first as mineral deposits of gypsum, used much in the fortification of breads, and the second as a constituent of cereals. Since both bread and cereals form a substantial part of the diet of the aged of the lower economic groups, the assimilability of these calcium compounds was considered to be of interest. Further, in order to simulate certain national dietaries such as Indian, American, and Irish, whole wheat flour, white flour, and potato flour were employed as carbohydrate sources.

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METHODS

A total of 160 weanling albino rats was distributed into 4 groups, as nearly identical as possible with respect to sex and litter (table 4). Each group received 1 of the 4 diets described below. From each of the 4 groups 6 males and 6 females were taken for ten day balance studies conducted at 30 to 40 day intervals up until 180 days of age and thereafter at intervals of 90 to 100 days up to 640 days. The urine and the feces were collectively analyzed. Toward the end of the experiment, when the animals died or became very ill, they were replaced by healthier rats of a comparable age and dietary origin; this may explain the small rise in the calcium balance observed at 462 days. Five days after the beginning of each balance period, 1 rat, generally of each sex, on each diet (selected from animals not on balance) was sacrificed for bone studies. Due to the decrease in the number of the animals through natural deaths, the sacrificing of animals was omitted after 270 days, except for 1 further sacrifice at approximately 460 days.

Diets.—Four different diets were employed (table 1):

Diet 1 (0.3% Ca-phytate +white flour)
Diet 2 (0.3% $CaSO_4$ +whole wheat flour)
Diet 3 (0.6% $CaSO_4$ +whole wheat flour)
Diet 4 (0.3% $CaSO_4$ +potato flour)

The flour constituted 69 per cent of each of the diets. The remaining 31 per cent consisted of a basic diet of the following composition: Brewers' yeast 10 per cent (1/10 irra-

diated), crude Argentine casein 5 per cent, salt mix 3 per cent,[1] cottonseed oil (commercial Wesson Oil) 10 per cent, cod liver oil 3 per cent. The protein content of each of the diets was 15 per cent.

TABLE 1. FORM AND LEVEL OF CALCIUM ADDITIONS

Diet No.	1	2	3	4
Carbohydrate	White Flour	Whole Wheat Flour	Whole Wheat Flour	Potato Flour
Calcium % Theoretical Value	0.3 as calcium phytate	0.3 as calcium sulphate	0.6 as calcium sulphate	0.3 as calcium sulphate
Average Analytical Value %	0.27	0.4	0.7	0.39
Calcium/ Phosphorus Ratio	1:2	1:1	2:1	1:1

Accepted analytic procedures described in A.O.A.C. Methods of Analysis (2) were employed for determinations of the moisture content of the diets and the air-dried excrement. The calcium analyses were made by a modification of Ingols and Murray's method (5). Density measurements (7) on the zein-coated bones (i.e., bones dipped in a saturated alcoholic solution of zein and then dried) made it possible to express calcium values of the femurs in terms of both weight percentage and grams per unit volume.

RESULTS

The results of the present experiment are discussed under Growth, Mortality, Calcium Balance, and Bone Calcification.

A. Growth

Growth differences, except among the males, were negligible (figs. 1 and 2).

[1] Modified Adolph's Salt Mixture (1) had the following composition: potassium chloride 41.56%, sodium chloride 34.93%, magnesium sulphate (septahydrate) 19.34%, ferrous sulphate (pentahydrate) 4.0%, sodium fluoride 0.12%, potassium iodide 0.01%, potash alum 0.02%, manganese sulphate (septahydrate) 0.04%, and copper sulphate (pentahydrate) 0.08%.

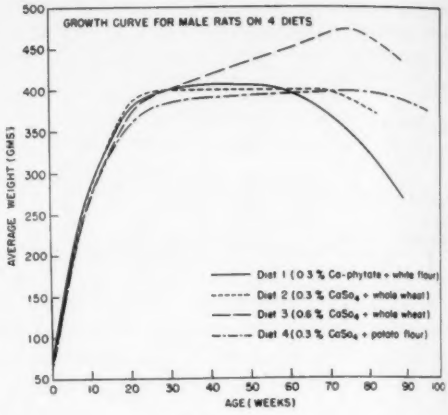
GROWTH CURVE FOR MALE RATS ON 4 DIETS
AVERAGE WEIGHT (GMS)
AGE (WEEKS)
Diet 1 (0.3 % Ca-phytate + white flour)
Diet 2 (0.3 % CaSO4 + whole wheat)
Diet 3 (0.6 % CaSO4 + whole wheat)
Diet 4 (0.3 % CaSO4 + potato flour)

Figure 1.

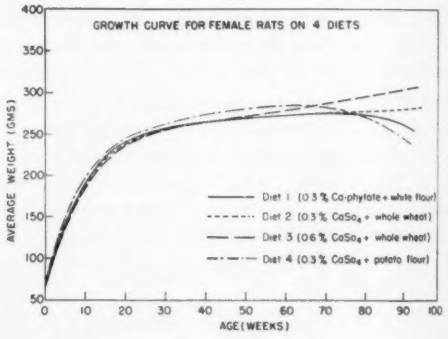
GROWTH CURVE FOR FEMALE RATS ON 4 DIETS
AVERAGE WEIGHT (GMS)
AGE (WEEKS)
Diet 1 (0.3 % Ca-phytate + white flour)
Diet 2 (0.3 % CaSO4 + whole wheat)
Diet 3 (0.6 % CaSO4 + whole wheat)
Diet 4 (0.3 % CaSO4 + potato flour)

Figure 2.

In the case of the males, the growth responses differed only on the high calcium diet No. 3. The maximum average weight attained by these animals was 475 Gm., whereas the corresponding figure for the other male rats on all other diets was 400 Gm. The females, on the other hand, exhibited no such striking difference. If, like humans, the growth requirement for male rats is greater than that of the females (8) it is possible that the lower level of calcium would suffice for the females and further increases would not result in greater growth; however, if the low level were insufficient for the males, greater growth would result from further increase of the calcium level. A higher feed intake and lower excretion of Ca in the case of the males

on diet No. 2 (whole wheat flour, low $CaSO_4$) during the first balance period seem to support this point of view. It was noted that the animals on the diet containing potato flour had a fur condition that was remarkably smoother in comparison to the animals on any of the other diets, especially in comparison to diet No. 1 (white flour, low calcium phytate). The animals on the latter diet were characterized by a roughness and yellow color of the fur.

B. Mortality

No significant differences in the mortality rate due to diet were observable at the 5 per cent level by analysis of variance, although there seemed to be a tendency for animals on the potato diet to have a shorter life span (tables 2 and 3).

TABLE 2. INDIVIDUAL LONGEVITIES IN DAYS.

Diet/Sex				Diet/Sex			
1/M	2/M	3/M	4/M	1/F	2/F	3/F	4/F
282	325	161	332	401	455	360	370
366	351	442	332	450	476	420	529
425	397	458	344	460	495	424	561
537	398	460	367	520	496	435	596
547	408	470	397	549	541	593	599
550	469	498	446	566	559	643	621
570	514	504	495	578	629	647	648
581	520	518	528	601	666	699	649
593	528	531	554	604	704	715	712
594	532	603	558	702	717	764	726
620	585	646	565	810	725	806	751
623	602	805	574	813	913	822	
670	603		616			822	
			630			933	
			671				

A difference in mortality with regard to sex was noted, however, the females outliving the males by 113 days.

C. Calcium Balance

The relative value of gypsum and phytin as sources of calcium is indicated by the accompanying data (figs. 3-6). It will be noted that there is greater calcium retention from gypsum as compared to phytin at the start of the experimental period; the animals on

TABLE 3. GROUPED LONGEVITIES IN DAYS.

	No. of Animals[1]	Mean Longevity	Means Corrected for Respective Sex, Litter, and Treatment Effects
Males	53	504	515
Females	49	617	605
Diet 1	25	560	564
Diet 2	25	544	562
Diet 3	26	579	572
Diet 4	26	555	542

[1] Further detail may be obtained from table 2.

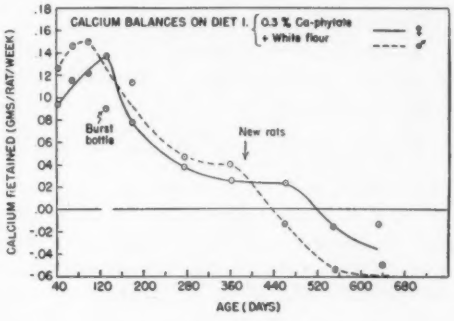

Figure 3.

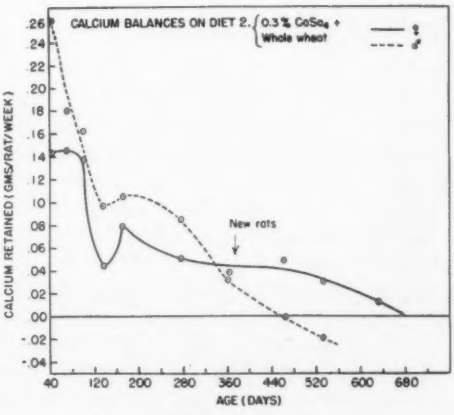

Figure 4.

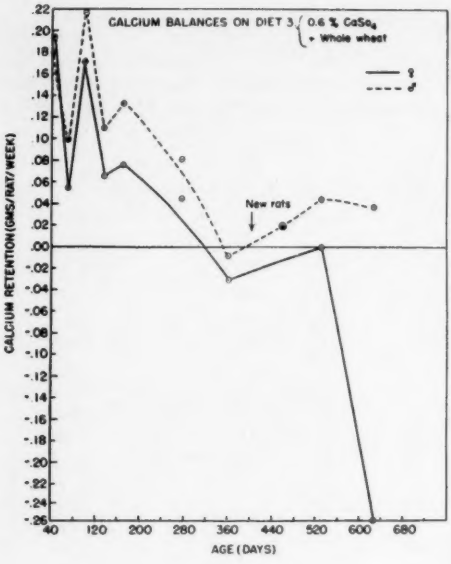

Figure 5.

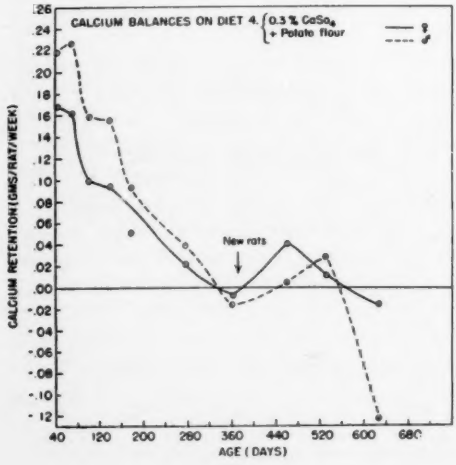

Figure 6.

the calcium sulphate (diet No. 2—whole wheat flour, low $CaSO_4$, and diet No. 4—potato flour, low $CaSO_4$) being in a more positive balance than those on the phytin (diet No. 1—white flour, low calcium phytate). Thus the availability of calcium in the gypsum must have been greater than in phytin, unless the carbohydrates of the respective diets in some way altered the degree of assimilation. Data on bone composition in section D throw further light on these points.

The turning point from a positive calcium balance to a negative one provided a great deal of information.

1. It was noted that animals on a more adequate diet with respect to calcium proceeded into a negative balance earlier than those on a lower calcium regime. The data of Hsu (4) tend to substantiate the same conclusions. Thus it was seen that animals on diets No. 1 (white flour, low calcium phytate) and 2 (whole wheat flour, low $CaSO_4$) went into negative balance later than those on diets No. 3 (whole wheat flour, high $CaSO_4$) and 4 (potato flour, low $CaSO_4$). These latter 2 diets would be expected to furnish a readily available supply of calcium since diet No. 4 lacks any appreciable amount of phytic acid and diet No. 3 has a level of calcium great enough to compensate for the phytic acid present in the whole wheat.

2. There was a tendency for males to precede the females in going into negative calcium balance, although for animals on diet No. 3 (whole wheat flour, high $CaSO_4$), the reverse was true.

3. It seemed that all animals on all diets were still in positive balance at 280 days, a time prior to which maturity is commonly assumed to have been attained. The fact that this may be due to calcium storage and bone growth will be discussed in section D.

Thus a positive state of the calcium balance may be misleading as a criterion of the health of the animals. What is important is the previous history of the animal with respect to calcium. It seems that, although the animal may be in positive calcium balance (e.g., the animals on diet No. 1—white flour, low calcium phytate), its total body calcium may be less than that of an animal in negative calcium balance, which has always received a diet rich in calcium, such as diet No. 3 (whole wheat flour, high $CaSO_4$). Interpretation of a state of calcium

nutrition, then, cannot be made from a mere knowledge of the positivity or negativity of the balance of the element; other factors such as the animal's age and sex, the form and level of the calcium supplied to it, and above all, the nutritional history must be considered. The latter point is also made by Hegsted and associates (3).

D. Bone Growth and Calcification

Significance of bone volumes: That bone growth occurs after 280 days is strongly indicated by a statistical analysis on pooled data involving average correlation between bone volume and age within the various treated groups. The correlation coefficient needed for significance at the 1 per cent level was 0.25, whereas in the data analyzed it was 0.48, indicating a high degree of significance. This finding is in agreement with observations by Hsu (4).

Upon resolving the data on bone volume into individual groups of sex and diet, it was found that increases in bone volume after the age of 280 days of males and females on diet No. 1, (white flour, low calcium phytate) were not significant at the 5 per cent level. Similar findings were revealed for the animals on diet No. 3 (whole wheat flour, high $CaSO_4$), although in this case, the non-significance was borderline. It is probable that these cases of non-significance were due to small samples, the number of available animals of each sex on each diet ranging from 13 to 18.

Thus the positive calcium balance after 280 days referred to in the foregoing section could possibly be attributed not only to storage, but also to bone growth. The latter is noteworthy, especially from the point of view of adult growth of the rat.

Significance of percentage of calcium per unit volume of bone: An analysis involving the method of least squares[1] was employed to obtain an unbiased estimate of the percentage of calcium per unit volume of bone, making corrections for sex, litter, and treatment effects. These data showed that, first, the sexes did not differ significantly in the percentage of calcium per unit volume of bone, although the females tended to have a greater calcium density, and, second, that the differences due to the 4 diets were highly significant at the 1 per cent level, the estimates corrected for sex and litter effects being as follows:

Diet 1 −2.30% calcium per unit volume
Diet 2 −0.19% calcium per unit volume
Diet 3 +1.19% calcium per unit volume
Diet 4 +1.30% calcium per unit volume

These values would also logically represent the relative availability of the calcium supplied in the diets as follows:

Diet 4 > Diet 3 > Diet 2 > Diet 1

The comparative equality of the availability of the calcium in diets No. 4 and 3 is to be noted. These data further substantiate the findings on the calcium balance data in section C regarding the greater availability of calcium from gypsum than from phytate, and the effect of phytic acid in decreasing the absorption of calcium.

[1] The method used is sometimes called the "method of fitting constants" and is described in a number of textbooks. It involves the solution to a set of simultaneous equations having right members which are sex, litter and treatment totals. The unknown or parameters which are to be solved for pertain to sex, litter and treatments. The coefficients of these unknowns in each equation are obtained by taking the expected value of the righthand member.

SUMMARY

The relative availability of the calcium present in four diets followed the order of:—diet 4 (potato flour, low $CaSO_4$) > diet 3 (whole wheat flour, high $CaSO_4$) > diet 2 (whole wheat flour, low $CaSO_4$) > diet 1 (white flour, calcium phytate).

Male rats on diet No. 3 (0.6 per cent calcium) reached an average maximum weight approximately 75 Gm. greater than on the other diets. Among the female rats no differences due to diet were found. A requirement greater than 0.3 per cent available calcium for male rats is postulated.

No significant difference in the mortality rate of male or female animals was found on the 4 diets.

The calcium of gypsum was more available than that of calcium phytate as observed both in balance studies and in investigations

TABLE 4. BONE VOLUME AND CALCIUM CONTENT WITH RESPECT TO AGE AND DIET.

Diet 1				Diet 2				Diet 3				Diet 4			
Number of Animals	Mean Age (Days)	Mean Bone Vol. (Cc.)	Mean Ca (Gm/ 100 Cc.)	Number of Animals	Mean Age (Days)	Mean Bone Vol. (Cc.)	Mean Ca (Gm/ 100 Cc.)	Number of Animals	Mean Age (Days)	Mean Bone Vol. (Cc.)	Mean Ca (Gm/ 100 Cc.)	Number of Animals	Mean Age (Days)	Mean Bone Vol. (Cc.)	Mean Ca(Gm/ 100 Cc.)
Males															
2	60	0.651	12.4	2	60	0.668	18.6	3	66	0.594	21.3	2	60	0.615	17.8
3	131	0.920	25.1	3	131	1.005	26.0	4	140	0.975	25.7	3	132	0.911	25.8
1	282	1.414	20.7	1	280	1.308	20.7	1	280	1.262	32.8	1	280	1.137	29.6
1	366	1.570	22.8	4	367	1.182	24.4	6	466	1.351	25.5	5	354	1.174	28.9
2	446	1.298	24.7	3	481	1.273	26.9	3	514	1.142	24.6	3	472	1.285	24.0
7	567	1.366	21.0	5	536	1.417	22.4	2	625	1.423	25.0	5	556	1.201	24.7
3	638	1.332	19.7	2	603	1.437	22.3	1	805	1.609	22.4	3	639	1.530	21.6
—				—				—				—			
19				20				20				22			
Females															
2	60	0.534	15.3	2	60	0.504	20.2	3	66	0.591	22.4	3	66	0.560	22.2
3	132	0.714	25.1	3	132	0.825	26.3	2	125	0.686	29.1	3	131	0.698	29.5
4	445	0.867	25.2	1	280	0.710	32.1	1	280	0.914	32.8	1	280	0.723	33.5
4	553	0.919	23.0	5	478	0.835	24.7	1	360	0.757	32.0	1	370	0.739	24.2
2	603	0.947	23.5	2	550	0.814	24.2	6	433	0.846	25.5	1	484	0.833	29.8
1	702	0.888	21.2	2	648	0.938	23.7	1	593	0.876	27.0	4	557	0.941	25.9
2	812	0.936	20.9	3	715	1.010	23.6	3	663	0.938	26.5	3	639	0.894	25.5
—				1	913	0.150	20.4	2	740	0.902	25.0	3	730	1.044	24.5
18				—				3	817	1.010	25.8	—			
				19				1	933	0.820	26.5	19			
								—							
								23							

Data were grouped according to age in intervals of 100 days.

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on bone calcification. Those animals given higher amounts of calcium tended to go into negative balance earlier than those receiving less calcium. In general, the males preceded the females in going into negative calcium balance.

The bone volume of the animals continued to increase after the age of 280 days.

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Data were grouped according to age in intervals of 100 days.

CALCIUM BALANCE IN ELDERLY WOMEN

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In a previous study on the calcium balance in elderly men (1) we found the equilibrium requirements for these subjects to be not only much higher than reported in the literature for young adults, but also higher than reported for elderly subjects. A discussion of these facts and references to the literature on the subject are found in the paper cited. We thought, therefore, that it would be desirable to study the calcium balance in a number of elderly women to determine if similar results would be obtained.

Material and Methods

The calcium balance investigation was conducted on 8 elderly women, all inmates of the St. Louis Chronic Hospital whose ages ranged from 48 to 83 years. All subjects were free of acute or infectious diseases at the beginning of the study. The Kahn test was negative and the fasting blood sugar and serum calcium were within normal limits. In none of the individuals was any marked evidence of osteoporosis noted in radiologic examination. The thyroidal and renal clearances of radioiodine were measured according to the method of Berson and associates (4). The thyroidal clearances were within the normal limits for all 8 persons but the renal clearances in 3 subjects were lower than the values observed by Berson in normal subjects. Other laboratory data and the results of the physical examinations are given below.

Subject No. 1 This 73 year old subject was moderately well nourished and the skin seemed in better condition than would be expected for her age. No gross abnormalities were noted on physical examination. The chest was clear, the heart was slightly enlarged to the right, and the heart sounds were clear but distant. No masses were noted in the abdomen, the extremities were not abnormal, and the reflexes were physiologic. The urinary excretion of radioiodine indicated some impairment of the kidney function, and the N.P.N. was 45 mg.%. The serum albumin was 5.0 Gm.% and the globulin 2.3 Gm.%. The red cell count was 5.5 million, the hemoglobin 13.2 Gm.%, and the white count 14,800 with a normal differential. The blood pressure was 150/90.

Subject No. 2 This subject was 71 years old. She was well nourished and cooperative. The skin was somewhat atrophic. Physical examination was essentially negative. The chest was resonant and the heart slightly enlarged with a grade I apical murmur. No masses were noted in the abdomen and the extremities and reflexes were normal. The N.P.N. was 32 mg.%. The serum albumin was 4.7 Gm.% and the globulin 2.6 Gm.%. The red cell count was 3.9 million with a hemoglobin of 11.2 Gm.%. The white cell count was 8,500 with a normal differential. The blood pressure was 145/80.

Subject No. 3 This 83 year old subject was well nourished. She had moderate senile psychosis but was cooperative. Physical examination revealed no gross abnormalities. The chest was clear and the heart sounds were good. Repeated radiologic examination of the chest revealed evidences of arrested tuberculosis. No masses were noted in the abdomen, and the extremities and reflexes were normal. The N.P.N. was 32 mg.%. The red cell count was 3.4 million with a hemoglobin of 7.7 Gm.%. The white cell count was 5,400 with a normal differential. The blood pressure was 130/75.

Subject No. 4 This subject was 68 years old. She was somewhat obese. She had some psychotic symptoms but was cooperative. Physical examination was not remarkable. The chest was clear and the heart sounds regular with a slight apical systolic murmur. No masses were noted in the abdomen. The extremities were not abnormal and the reflexes were physiologic. The N.P.N. was 34 mg.%. The serum albumin was 4.4 Gm.% and the globulin 1.5 Gm.%. The red cell count was 4.7 million with a hemoglobin of 13.3 Gm.%. The white cell count was 4,700 with a normal differential. The blood pressure was 190/110.

Subject No. 5 This subject was 77 years old and fairly well nourished. She had some mental dullness but was cooperative. Physical examination revealed no gross abnormalities. The chest was clear and the heart sounds of good quality. No masses were noted

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in the abdomen, the extremities were not abnormal, and the reflexes were physiologic. The N.P.N. was 32 mg.%. The serum albumin was 4.6 Gm.% and the globulin 3.3 Gm.%. The red cell count was 4.1 million with a hemoglobin of 9.8 Gm.%. The white cell count was 9,600 with a normal differential. The blood pressure was 140/70.

Subject No. 6 This 80 year old subject was moderately well nourished and seemed younger than the stated age. Physical examination revealed no gross abnormalities. The chest was clear, the heart was slightly enlarged to the left, and the heart sounds were of good quality. No masses were felt in the abdomen, but the liver was just palpable below the costal margin. The extremities and reflexes were not abnormal. The N.P.N. was 33 mg.%. The serum albumin was 4.4 Gm.% and the globulin 2.5 Gm.%. The red cell count was 4.5 million with a hemoglobin of 14.0 Gm.%. The white cell count was 6,600 with a normal differential. The blood pressure was 145/90.

Subject No. 7 This subject was only 48 years old but she was at least five years past menopause. She was fairly well nourished and cooperative although unable to speak clearly. Physical examination revealed slight residual left hemiplegia from a stroke four years previous. The chest was clear, the heart was slightly enlarged to the left, and the heart sounds were of good quality. No masses were noted in the abdomen. Except for the residual evidences of the hemiplegia the extremities and reflexes were not abnormal. The urinary excretion of radioiodine gave evidence of some impairment of the kidney function but the N.P.N. was 33 mg.%. The serum albumin was 4.9 Gm. % and the globulin 2.2 Gm. %. The red cell count was 4.4 million with a hemoglobin of 12.0 Gm.%. The white cell count was 5,000 with a normal differential. The blood pressure was 170/100.

Subject No. 8 This 77 year old subject was moderately well nourished and the skin was in better condition than would be expected at that age. The subject had suffered fractures of the ankles and left hip some ten years previously and was now ambulatory with crutches. Physical examination revealed moderate kyphoscoliosis of the dorsal spine and some dullness to percussion over the left lower lobe. The heart was slightly enlarged to the left with some systolic murmur. No masses were noted in the abdomen and the liver was just palpable below the costal margin. The urinary excretion of radioiodine indicated some decrease in kidney function and the N.P.N. was 44 mg.%. The serum albumin was 4.1 Gm.% and the globulin 2.7 Gm.%. The red cell count was 4.3 million with a hemoglobin of 12.6 Gm.%. The white cell count was 5,100 with a normal differential. The blood pressure was 145/95.

The subjects were on an accurately regulated diet with an intake of 1.0 Gm. of protein and approximately 35 calories per kilogram body weight throughout the investigation. During the whole test period the subjects were in a positive nitrogen balance of from 10 to 27 mg. of nitrogen per kilogram per day, with an average positive balance of 19 mg. per kilogram per day. The diets used were well balanced and contained meats, eggs, and milk as well as fresh and canned vegetables. The diets were considered by us and by the subjects to be superior to the regular hospital diet. The basic menus were similar to No. 3 of our earlier study (6) with additional meat and milk where required to give more protein. The basic diet was estimated to contain approximately 100 to 150 I.U. of vitamin D per day, and this would be the amount received by the subjects, who weighed between 40 and 42 Kg. The heavier subjects, who weighed between 55 and 65 Kg., received additional protein and milk and thus somewhat more vitamin D, the heaviest subject (75 Kg.) receiving approximately 250 I.U. daily.

As indicated in table 1, subjects 1, 2, 5, and 6 were tested on 3 levels of calcium intake and the others on 2 levels. The second level for the former subjects and the first level for the others corresponded to the regular diet. The highest calcium intake level in all subjects corresponded to the regular diet plus added calcium gluconate equivalent to 255 mg. of calcium per day. The lowest level of calcium intake in subjects 1, 2, 5, and 6 was on a diet similar to the regular diet except that it contained somewhat less milk, other proteins being added to keep the nitrogen intake constant.

The details of the diets, balance procedures, control of food intake, and collection of samples were the same as used in our previous studies (1, 6). The calcium analysis was performed by the flame photometric method as given in detail in an earlier publication (2).

Duplicate samples, each equivalent to the total basic diet offered for the day, were analyzed each day. The urine specimens, stool specimens, and foods left were pooled

separately for each patient for five day periods for analysis. In all our calcium balance studies we have noted considerable variations in the fecal calcium from period to period due possibly to minor changes in intestinal activity. Since as much as 80 per cent of the excreted calcium may be in the stool, this would mean considerable period to period variation in the calcium balance. For this reason we believe that calcium balances taken over short periods have little value and have used averages over periods of at least forty days.

Results

The results of the calcium balance studies are given in table 1 and figure 1. There was an equilibrium period of fifteen days or more on each intake level before the balance study was begun.

In the figure the intake in milligrams of calcium per kilogram body weight per day is plotted against the balance in the same units. The regression line, calculated by the method of least squares, intersects the horizontal axis at an equilibrium intake of 16.7 mg./Kg. The dashed line in the figure represents the regression curve obtained earlier on the men (1). It leads to a somewhat higher equilibrium value of 18.6 mg./Kg. During the course of our experiments we have at times determined the calcium balances on elderly women and men at the same time and on exactly the same diet and the requirements of the women have been consistently lower.

Table 1. Calcium Balance in Elderly Women

Subject	Age	Average Weight (Kg.)	Duration of Balance Period (Days)	Intake	Excretion		Balance	Intake	Balance
					Urine	Stool			
				mg./day				mg./Kg./day	
1	73	74.5	40	1192	161	1140	—119	16.0	—1.4
		74.7	60	1360	216	1152	— 8	18.3	—0.1
		75.5	45	1625	156	1306	+161	21.5	+2.1
2	71	40.8	40	428	90	456	—118	10.4	—2.9
		41.3	60	658	93	521	+ 44	16.0	+1.1
		41.8	45	910	86	726	+ 98	21.8	+2.4
3	83	63.5	60	1111	86	983	+ 42	17.5	+0.7
		64.0	45	1360	119	1065	+176	21.3	+2.8
4	68	59.0	60	1078	174	891	+ 13	18.2	+0.2
		59.2	45	1325	163	976	+186	22.4	+3.1
5	77	43.2	40	448	114	669	—142	10.4	—3.3
		43.2	60	518	114	505	—101	12.0	—2.3
		43.0	45	785	110	657	+ 18	18.3	+0.4
6	80	42.0	40	497	113	505	—121	11.8	—2.9
		42.2	60	619	123	547	— 51	14.6	—1.2
		42.2	45	889	120	692	+ 77	20.9	+1.8
7	48	64.2	60	1055	196	880	— 21	16.5	—0.3
		64.4	45	1328	185	970	+173	20.6	+2.7
8	77	55.5	60	797	131	741	— 75	14.4	—1.4
		56.0	45	1060	117	848	+ 95	18.9	+1.7

(See text for explanation)

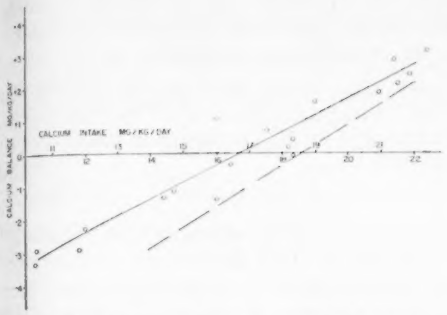

Fig. 1. Calcium intake and balance in 8 elderly women. Data from table 1 plotted as milligrams of calcium per kilogram body weight per day. Regression line calculated by method of least squares.

Discussion

As pointed out in our earlier discussion of the calcium balance in elderly men (1) the equilibrium values reported for young adults range from 8 to 12 mg./Kg./day of calcium, and some reports on elderly subjects lead to essentially the same values. The animal experiments of Kane and McCay (5) would lead to an expectation of higher calcium requirements in older subjects. The existence of post-menopausal osteoporosis as a definite clinical entity (3) would also lead to an expectation of increased negative calcium balance in elderly women. Our results are consistent with these views, since we find a higher calcium requirement for our elderly women than has been reported for younger women, and somewhat higher than the value of 14.3 mg./Kg. reported by Ohlson and associates (8) for elderly women, and the average figure of 14.1 mg./Kg. computed from the work of Roberts (9). In at least some of the subjects studied by other investigators (for instance in the study by Roberts) additional vitamin D was administered, which may have decreased the calcium requirements, as we have found to be the case with men (2). Another factor, more difficult to control, which may influence the calcium balance in elderly subjects, is their previous dietary history and calcium intake (7). Although our subjects did not show any marked evidences of osteoporosis on radiologic examination, their past diet may not have been too adequate in calcium, since they were generally from the lower economic strata. However, we believe that the data do indicate an increased calcium requirement in elderly women.

Summary

The calcium balance was determined in 8 elderly women ranging in age from 48 to 80 years. An equilibrium intake of 16.7 mg./Kg./day of calcium was found, somewhat higher than the value of 14.3 reported by others for similar subjects and much higher than values reported for young adults.

Acknowledgement is made to Dr. W. B. Kountz and Dr. T. Kheim, who conducted the physical examinations of the subjects.

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THE EFFECT OF SEX HORMONE ADMINISTRATION ON THE CALCIUM AND NITROGEN BALANCE IN ELDERLY WOMEN

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EARLIER work in this laboratory has indicated that the nutritional requirements of elderly individuals may differ from those of young adults. Elderly subjects require a larger intake of protein (7, 8) and calcium (1, 3) for balance than do the younger. It was also found that in elderly men the administration of testosterone produced a positive nitrogen balance (6). Other work has indicated that the administration of estrogens and androgens to elderly women had a favorable effect on their clinical (9) and mental (5) status. As a continuation of our studies on the nutritional requirements in the aged it was considered of interest to study the effect of estrogen, androgen, and progesterone therapy on the calcium and nitrogen balance in elderly female subjects.

MATERIALS AND METHODS

The study included 7 elderly women, all inmates of the St. Louis Chronic Hospital. They are the same subjects, numbers 1 to 7, used in our earlier study (3). Subject No. 8 of the previous study was not used here. The details of the physical examination and laboratory tests may be found in the earlier publication cited above. It may be noted here that all the subjects were free of acute or infectious diseases at the time of the test, none showed any marked degree of osteoporosis on radiologic examination, all had normal serum calcium levels, and none showed any marked thyroid dysfunction as indicated by radioiodine uptake. Subjects 4 and 7 had some hypertension and subjects 1 and 7 showed some evidence of impaired kidney function. No gross abnormalities were noted on physical examination. All the subjects were examined by a gynecologic consultant. Pelvic examination was essentially negative except in subject No. 4, who showed some slight vaginal bleeding and cervical erosion. This subject did not receive any hormone therapy but served as a control.

The subjects were on the same diet as used previously (3) through the entire study period. This diet contained 1 Gm. of protein and approximately 35 calories per kilogram body weight per day. The calcium intake varied from 12 to 19 mg. per kilogram per day for the different subjects but was constant to within plus or minus 15 per cent for each five day period for each subject. The foods offered were analyzed daily in duplicate samples. The urine specimens, stool specimens, and foods left were pooled separately for analysis for each subject for five day periods. The foods offered were analyzed for nitrogen daily throughout the entire study period as a check on the constancy of the intake, but the complete analyses for calcium and nitrogen of all specimens were made only for those periods for which the balance was to be computed as mentioned below. The calcium analyses were performed by the flame photometric method as outlined in detail in a previous publication (2). The general details of balance procedure, control of food intake, collection of samples, and nitrogen analysis were the same as used in our previous studies (1, 8).

The calcium intakes, outputs, and balances were first computed in milligrams of calcium per day averaged over the entire balance period. Later, for comparison, the results were expressed as milligrams of calcium or nitro-

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gen per kilogram body weight per day and plotted according to the method of Reifenstein (11) as used in our earlier publications on calcium balance, a projection of the vertical column above the base line representing a negative balance.

Hormone Treatment and Results

The results of the studies are given in table 1 and figure 1. In the table under the heading "Days" are given the total number of days during which the subjects received the medication given in the adjoining column, and the number of days during which the specimens were analyzed and the balances computed. The balances were always taken during the latter part of each medication period, the earlier portion being allowed for adjustment. For example, if an individual received the medication for 120 days and the balance was computed for a 60 day period, the first 60 days of the medication period would be allowed for adjustment. In the table are given also the average intakes, outputs, and balances during the balance period as well as the average weight of the subjects during that time. In the figure the dotted shaded area at the bottom of each column represents the urinary output and the diagonally shaded area at the top the fecal output.

In all individuals the first period represents an initial period without any hormone therapy. After this period, each subject, except No. 4, who received no medication at

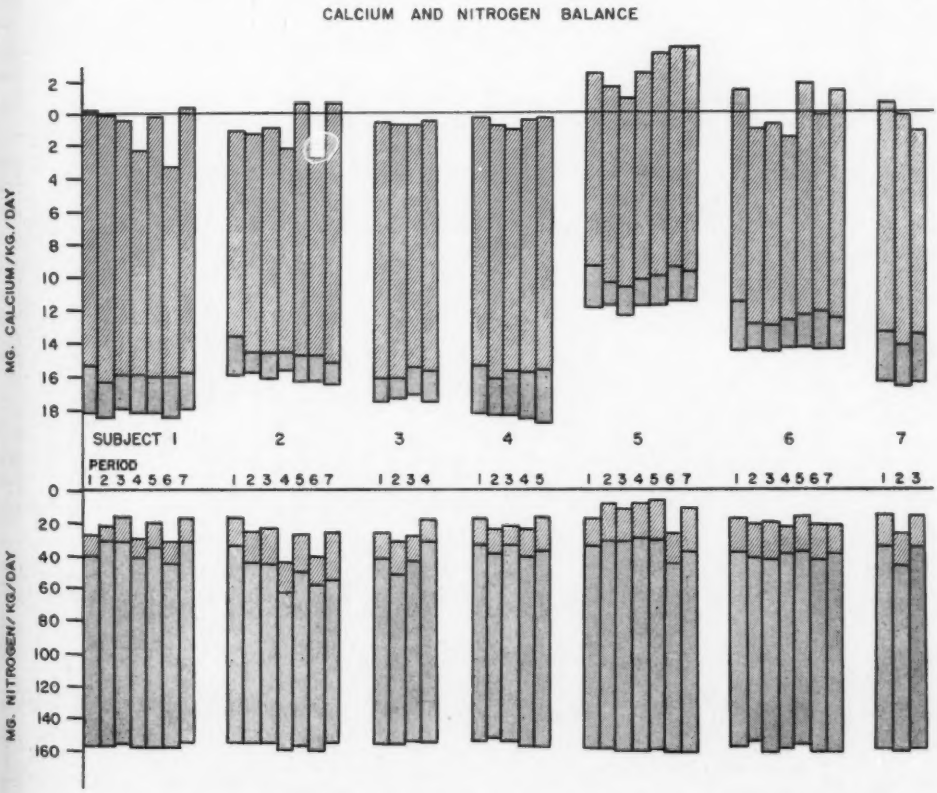

Fig. 1. Calcium and Nitrogen Balances in Elderly Women. See text for details of hormonal therapy in the different periods.

TABLE 1. CALCIUM AND NITROGEN BALANCES UNDER HORMONE ADMINISTRATION

Period	Total Length of Period (Days)	Length of Balance Period (Days)	Medication	Average Weight Kg.	Calcium Balance Mg./Day Output				Nitrogen Balance Gm./Day Output			
					Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
			Subject No. 1—Age 73 years									
1	90	60	No medication	74.7	1360	216	1152	— 8	11.79	8.84	0.94	2.04
2	120	60	Estrogen	77.1	1430	175	1247	8	12.15	9.75	0.79	1.61
3	120	50	Estrogen—menstruation	80.6	1452	167	1246	39	12.63	9.75	1.33	1.33
4	40	30	Estrogen—androgen	83.0	1512	192	1131	189	13.20	9.71	0.99	2.49
5	80	60	Estrogen	84.1	1528	174	1343	11	13.35	10.43	1.19	1.71
6	40	30	Estrogen—androgen	86.0	1582	202	1098	282	13.73	9.70	1.26	2.74
7	70	40	Estrogen	86.0	1550	186	1386	—22	13.24	10.52	1.14	1.58
			Subject No. 2—Age 71 years									
1	90	60	No medication	41.3	658	93	521	44	6.36	4.89	0.72	0.75
2	120	60	Estrogen	43.2	684	46	584	54	6.70	4.71	0.90	1.09
3	120	50	Estrogen—menstruation	43.5	707	72	593	38	6.76	4.69	1.06	1.01
4	40	30	Estrogen—androgen	43.5	685	46	547	92	6.95	4.24	0.77	1.94
5	80	60	Estrogen	44.7	735	75	693	—33	7.07	4.85	0.97	1.25
6	40	30	Estrogen—androgen	46.5	761	72	559	130	7.52	4.84	0.77	1.91
7	70	40	Estrogen	47.5	796	90	837	—31	7.47	4.95	1.21	1.31
			Subject No. 3—Age 83 years									
1	80	50	No medication	63.5	1111	86	983	42	9.97	7.20	0.98	1.79
2	100	40	Estrogen	66.5	1153	84	1020	49	10.53	6.96	1.41	2.16
3	100	40	Estrogen—menstruation	69.5	1195	120	1016	59	10.84	7.76	1.05	2.03
			Subject No. 4—Age 81 years									
1	60	40	No medication—control	59.0	1078	174	891	13	9.22	7.21	0.88	1.13
2	60	40	No medication—control	59.5	1101	145	903	53	9.14	6.72	0.86	1.56
3	70	40	No medication—control	60.0	1107	165	873	69	9.40	7.32	0.77	1.31
4	70	40	No medication—control	60.5	1125	172	921	32	9.66	7.13	1.08	1.45
5	60	40	No medication—control	61.0	1152	189	951	12	9.77	7.47	1.22	1.08

TABLE 1.—Continued. CALCIUM AND NITROGEN BALANCES UNDER HORMONE ADMINISTRATION

Period	Total Length of Period (Days)	Length of Balance Period (Days)	Medication	Average Weight Kg.	Calcium Balance Mg./Day Output				Nitrogen Balance Gm./Day Output			
					Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
			Subject No. 5—Age 77 years									
1	90	60	No medication	43.2	518	114	505	—101	6.93	5.36	0.78	0.79
2	120	60	Estrogen	42.6	506	60	513	—67	6.83	5.46	0.94	0.43
3	120	50	Estrogen—menstruation	42.2	521	70	486	—35	6.81	5.47	0.82	0.52
4	40	30	Estrogen—progesterone	42.0	500	71	528	—99	6.81	5.55	0.89	0.37
5	80	60	Estrogen	41.6	495	79	572	—156	6.72	5.39	1.02	0.31
6	40	30	Estrogen—progesterone	41.1	476	80	557	—165	6.77	4.75	0.91	1.10
7	70	40	Estrogen	40.7	475	68	585	—167	6.66	5.04	1.16	0.46
			Subject No. 6—Age 80 years									
1	90	60	No medication	42.2	619	123	547	—51	6.71	5.04	0.88	0.79
2	120	60	Estrogen	43.5	627	63	517	47	6.80	4.93	0.91	0.96
3	120	50	Estrogen—menstruation	45.4	666	75	549	42	7.44	5.44	1.10	0.90
4	40	30	Estrogen—progesterone	47.4	683	80	523	80	7.65	5.67	0.88	1.10
5	80	60	Estrogen	48.5	702	97	693	—88	7.67	5.76	1.10	0.81
6	40	30	Estrogen—progesterone	49.2	717	118	591	8	7.96	5.76	1.14	1.06
7	70	40	Estrogen	49.5	721	112	665	—56	8.01	6.04	0.90	1.07
			Subject No. 7—Age 48 years									
1	80	60	No medication	64.2	1055	196	880	—21	10.28	8.00	1.22	1.06
2	100	60	Estrogen	65.0	1085	158	916	11	10.38	7.31	1.39	1.68
3	100	40	Estrogen—menstruation	66.0	1095	186	834	75	10.52	8.12	1.41	0.99

(See text for explanation.)

any time and served as a control, was given 1 mg. of estradiol benzoate in oil intramuscularly twice weekly for the time indicated in the table, the balance being computed for the last 40 or 60 days of the medication period. Menstruation was then induced in subjects 1, 2, and 3 by the cyclic withdrawal of the estradiol benzoate during one week of each month, and in subjects 5, 6, and 7 by the cyclic administration, during continued estrogen therapy of 10 mg. of progesterone intramuscularly for 3 successive days each month. Moderate bleeding of five to ten days duration occurred in all subjects. The menstrual blood was collected on sanitary pads which had been tested and found to be nitrogen and calcium free. This material was not analyzed separately but pooled with the stool samples for the respective periods used in calculating the balances.

An inspection of table 1 and figure 1 shows that subjects 1, 2, and 3, who were in positive nitrogen balance and in calcium equilibrium or positive balance during the initial period, showed no marked change in calcium or nitrogen balance with the estrogen therapy or induced menstruation (periods 2 and 3). Only subject No. 1, who was initially in calcium equilibrium, showed any increase in calcium retention. Subjects 5, 6, and 7, who were initially in negative calcium balance, did show some increase in calcium retention during periods 2 and 3 (estrogen therapy). These subjects were also initially in positive nitrogen balance and the administration of the estrogen had little effect on this balance.

The effects of large doses of testosterone and progesterone on the calcium and nitrogen balances were studied subsequently. In period 4, subjects 1 and 2 received 30 mg. of testosterone daily for thirty days and in period 6 they received 20 mg. of testosterone daily and 1 mg. of estradiol benzoate twice weekly. In periods 5 and 7 they received only the twice weekly dosage of estradiol benzoate. All hormones were given intramuscularly. It will be noted that the testosterone has a noticeable effect on both the calcium and nitrogen balances in both subjects, increasing the retention of the two elements.

Subjects 5 and 6 received a similar treatment with the substitution of progesterone for the testosterone. It will be seen that there was less effect on the balances in either subject. Subject 5 showed an increased nitrogen retention in period 6 but no other change and an actual decrease in calcium retention during therapy. Subject 6 showed some tendency toward an increased calcium retention during the hormone administration, but the nitrogen balance did not change.

It will be noted from the table that with the beginning of the estrogen therapy there was a marked decrease in urinary calcium in the majority of the subjects. All of the subjects were on a controlled diet and their fluid intake and urinary volume did not change greatly at any time during the test. In subjects 1, 2, 5, and 6 there was a significant lowering of urinary calcium with the beginning of the hormone therapy which persisted through several experimental periods. Because of the relatively small proportion of the total calcium excreted in the urine, this change in urinary calcium had little effect on the balance, or was compensated for by relatively small percentage changes in the fecal excretion.

Discussion

Although the dosages of estrogens used in the earlier part of the studies were sufficient to produce clinical and mental improvement in the subjects as reported in other publications (5, 9), it had no effect on the nitrogen balance in subjects who were already in positive balance. While not shown in the averages, when the estrogen therapy was first started the subjects usually had a slight increase in nitrogen retention, which however returned to the pre-medication level within a few weeks. The dosage of estrogen also had little effect on the calcium balance in subjects already in positive calcium balance. The effect was not very great even on the subjects in negative calcium balance. The dosage may have been too small to produce any

striking effect. Albright (4) in some studies on post-menopausal osteoporosis found that in 2 subjects receiving 5 mg. of estradiol benzoate per week there was a marked increase in nitrogen and calcium retention while there was no change in 1 subject who received 3 mg. per week. Our subjects received only 2 mg. per week. By the time the third balance period was begun subjects 1, 2, 5, and 6 had been receiving the estradiol for over four months. Clinical response to estrogen therapy is usually apparent within that time although it may take longer to build up to a maximum (10). The psychologic tests were made after a period of six months on therapy.

The administration of testosterone did produce significant calcium and nitrogen retention in 2 subjects. We had shown earlier that this hormone has a protein-sparing effect in elderly men (6). Other studies have also indicated that combined estrogen-androgen therapy in elderly women produces better clinical results (10). The substitution of progesterone for the estrogen had an effect in only 1 of the 2 subjects (in subject 5 but not in subject 6).

Summary

The nitrogen and calcium balances were determined in 6 elderly women before and during sufficient estrogen therapy to reinduce menstruation. No effect was noted in the nitrogen balance on any of the subjects, all of whom were initially in positive balance. There was little effect on the calcium balance in subjects initially in positive balance, but some increased retention in subjects initially in negative balance. Large doses of testosterone produced a marked increase in nitrogen and calcium retention; similar doses of progesterone had less effect.

All hormones used in this study were furnished through the courtesy of Schering Corporation.

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AGING AND MORTALITY FROM THERMAL INJURY

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THE older the man, the less capable is he of withstanding an injury—is a generalization having little objective supportive evidence, excepting the data collected by Bull and Squire (3) in England and Scotland.

Data concerning the death-rates attendant upon burns and scalds were gathered in Dallas, Texas, between 1944 and 1952; these are tabulated in table 1. These data permit a partial analysis of the effect of aging upon the mortality associated with thermal injury in the United States.

The Berkow method of estimating the extent of the burn or scald was used. Only areas of partial and full-thickness injuries were included in the area-estimate; first degree trauma was not. Only individuals definitively treated entirely within the confines of the Parkland Hospital are included in the statistics; since to include persons transferred into this hospital after treatment had been given elsewhere would bias the sample. For example, a person with burns covering 60 per cent of his body is treated in another hospital for two weeks prior to his transferal to Parkland where he ultimately recovers and is counted as a triumph. But—during five years he is the only one living of 9 persons burned as he was and treated in the hospital from which he was transferred. Should he be included in the Parkland burn-population, without taking cognizance of the 8 others similarly burned and treated in X hospital who died, the mortality associated with an average 60 per cent thermal injury at Parkland would have been 80 per cent (12/15); while in truth, the combined experiences in Hospital X and Parkland showed a mortality of 87 per cent (20/23) with thermal injuries covering 55 to 65 per cent of the body's surface.

All deaths occurring after a burn or scald before the discharge of the person from the hospital were counted as burn-deaths even though the cutaneous wounds may have completely healed. Scalds and burns were not separated for this analysis.

The homogeneity of the frequency-distributions of the various age groupings listed in table 1 was tested with the use of the χ^2 test as employed for the testing of homogeneity of two or more frequency-distributions by Brandt and Snedecor(2). Table 2 contains the results of this testing. Clearly, all age groupings could well have come from the same burn-population. The probabilities that the distributional variations were due to random fluctuations are 0.1 or greater. In other words, the observed differences in the distributions of the areas of injury between the age groupings are ascribable to chance and the various age groups can be considered as samples drawn from a single burn-population.

The method of probit analysis developed by Bliss (1) was used to test the hypothesis that chance accounts for the variations between the death-rates attending comparable thermal injuries among various age groups. Bull and Squire (3) first employed probit analysis for this particular purpose. The results of this analysis are shown in table 3.

The mortality curves in figure 1 were derived from the probit equations of column 5 of table 3. Table 1 of reference 3 was employed to convert probits to per cent mortality.

DISCUSSION

The position as well as the slope of the mortality-area of injury curves derived from the experience with burned and scalded in-

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TABLE 1. DATA—SUMMARY

Series	Age Limits	Number	Surface Area Injured (2nd and 3rd Degree) % of Body Surface—Berkow								
			5–14	15–24	25–34	35–44	45–54	55–64	65–74	75–84	85–94
I Dallas 1944–1951	61 and greater	Total	19	13	3	0	1	0	1	1	4
		Dead	9	9	2	0	1	0	1	1	4
II Dallas 1944–1951	0 – 61	Total		86	34	26	12	14	7	5	4
		Dead		1	3	7	5	12	6	5	4
III Dallas 1944–1951	15 – 61	Total		47	15	21	8	7	4	2	4
		Dead		1	3	6	3	5	4	2	4
IV Dallas 1944–1951	0 – 15	Total		39	19	5	4	7	3	3	0
		Dead		0	0	1	3	7	2	3	0
V Dallas 1944–1951	0 – 61 (long contact)	Total		47	15	14	12	11	5	5	3
		Dead		1	1	8	5	11	4	5	3
VI Dallas 1944–1951	0 – 61[1] (short contact)	Total		32	12	12	0	0	0	0	1
		Dead		0	0	0	0	0	0	0	1
VII Dallas 1944–1951	40 – 61	Total	18	10	4	9	3	1	1	2	
		Dead	1	1	1	5	2	1	1	2	
Dallas 1944–1951 plus Birmingham	61 and greater	Total	29	19	7	2	100% Mortality				
		Dead	14	14	7	2					
Birmingham[2]	61 and greater	Total	15	9	9	2	1	1	1	0	0
		Dead	7	7	9	2	1	1	1	0	0

[1] Sum of Series V and VI does not equal Series II because of inability to determine the duration of contact in a number of cases.

[2] Taken from figure 2, page 163, *Ann. Surg., 130:* 1949, Bull and Squire.

dividuals above and below the ages of 61 years in Dallas, Texas, differ significantly. The LD 50 of thermal injury for individuals 61 years old and older was one covering 13.4 ± 7.2[1] per cent of the body surface while the LD 50 for individuals under the age of 61 years was 49.16 ± 3.4 per cent of body surface.

[1] ± 1.96 x standard error of LD 50
or ± 1.96 $\sqrt{\text{Variance of } \bar{X}}$, X=area of injury in per cent body surface.

The probability that the LD 50 doses of thermal injury for populations above and below the age of 61 differ because of random variation is practically nihil. The fiducial limits of the LD 50 for the 2 populations are widely separated. The LD 50 doses of thermal injury for the same 2 age parameters calculated from the British data of Bull and Squire (3) practically coincide with those determined from the American data (see

TABLE 2. CALCULATION OF χ^2 FOR THE FREQUENCY DISTRIBUTION OF 2 SERIES OF SERIOUS[1] THERMAL INJURIES, ONE MADE UP OF INDIVIDUALS AGED 2 TO 15 YEARS, AND THE OTHER OF THOSE AGED 15 TO 61 YEARS. THE CLASS INTERVAL IS BASED UPON THE EXTENT OF INJURY EXPRESSED AS PER CENT OF BODY SURFACE WITH SERIATION AT 10 PER CENT INTERVALS.

Class Intervals – Percentile Ranks –	Number of Injuries Age—Years		$P = \frac{a}{a \text{ plus } a^1}$	aP
	2 – 15 (a^1)	15 – 60 (a)		
15 – 24	30	47	.610389	28.688283
25 – 34	15	15	.500000	7.500000
35 – 44	5	21	.807692	16.961532
45 – 54	3	8	.727272	5.818176
55 – 64	7	7	.500000	3.500000
65 – 74	3	4	.571428	2.285712
75 – 84	3	2	.400000	.800000
Total	$n_2 = 66$	$n_1 = 104$		aP 65.553703
			$\bar{P} = .61176$	

General formula: $\chi^2 = \frac{1}{\bar{P}\,\bar{Q}} \left(\lesssim (ap) - n_1 \bar{P} \right)$

$\bar{P} = \frac{n_1}{n_1 \text{ plus } n_2}$, $P = \frac{a}{a \text{ plus } a^1}$, $\bar{Q} = 1. - \bar{P}$

$$\chi^2_0 = \frac{1}{.61176 \times .38824} [65.553703 - (104)(.61176)]$$

$\chi^2_0 = 8.126$ P $> .2$ for n = 6

χ^2 .2 = 8.558

χ^2 .3 = 7.231

χ^2 of 5 series of serious burns calculated in the manner illustrated above.

Series Compared (ages)	χ^2 of frequency distributions of col. 1	P	χ^2 of P. — col. 3 (Fisher & Yates)	Degrees of freedom (n)
(2–15) : (61+)	8.957	$< .2$	8.558	6
(15–61) : (61+)	7.85	$< .3$	7.231	6
(2–15) : (0–2)	5.3026	.5	5.348	6
(2–15) : (40–61)	11.34	$< .1$	10.645	6
(15–61) : (0–15)	5.698	$< .5$	5.348	6
(2–15) : (15–61)	8.125	$> .2$	8.558	6

[1] Thermal injuries of second and third degree covering 15 per cent or more of the body.

TABLE 3. SUMMARY OF PROBIT ANALYSIS

Section	Series	LD 50	Fiducial Limit LD 50		Y = a + b X
	Ages	% Body Surface	$1.96\sqrt{V(X)}$	% Body Surface	
Dallas, Texas 1944 – 1951					
I	0 to 15	49.3	± 13.4	36 – 62	Y = (–) .0088 + .1016 X
	2 to 15	49.9	± 15.7	33 – 65	Y = .1999 + .0961 X
	15 to 61	45.6	± 3.68	42 – 49	Y = .7420 + .0942 X
	0 to 61	49.16	± 3.4	45 – 52	Y = 1.362 + .074 X
	61+	13.4	± 7.2	6 – 20	Y = 1.7291 + .2366 X
	0 to 61 (long contact)	44.07	± 4.1	44 – 48	Y = 1.28 + .084 X
	40 to 61	36.6	± 6.958	29.64 – 43.94	Y = 2.1748 + .07701 X
Bull [3]					
II	0 to 15	51		43 – 64	Y = 1.29 + .0728 X
	15 to 45	43		37 – 55	Y = 1.94 + .0709 X
	45 to 65	22.3		17 – 40	Y = 1.97 + .1343 X
	65+	12.34		6 – 15	Y = 3.61 + .1532 X
Bull [3] plus Dallas					
III	0 to 2	37.7	± 9.6	28 – 47	Y = 1.1104 + .1032 X
	2 to 15	50.04	± 5.24	45 – 55	Y = 1.2969 + .0774 X
	15 to 61	46.8	± 4.4	42 – 51	Y = 2.1044 + .0618 X
	61+	12.85	± 2.52	10 – 15	Y = 3.2457 + .1442 X

table 3). The fact that there is no overlap of fiducial limits, and that there is very close agreement between separate British and American experiences, indicates that the aging process, and not random variation, is the factor responsible for the differences between the LD 50's of 2 burn-populations: one above and the other below the 60th year.

The relatively small LD 50 of thermal injury for a burn-population after the 60th year of life has passed only signifies that an old individual cannot withstand as large a burn as a young individual. The effect of aging upon the increment of mortality (y) relative to unit-increment of injury (x) can be determined only by the comparison of the slopes of the respective mortality curves. After the 60th year the rate with which probit y increases per unit increase in area of injury is .2366X (X = unit area injury) and before the 60th year probit y increases more slowly at the rate of .074X.

Chi-square analysis of slope variance employing the equation

$$\chi^2 \text{ of slopes} = \frac{(b_1 - b_2)^2}{\frac{1}{A_1} + \frac{1}{A_2}}$$

$$\left(\frac{1}{A} = \frac{1}{[WX^2] \text{ of Bliss (3)}}\right)$$

shows that the probability of random varia-

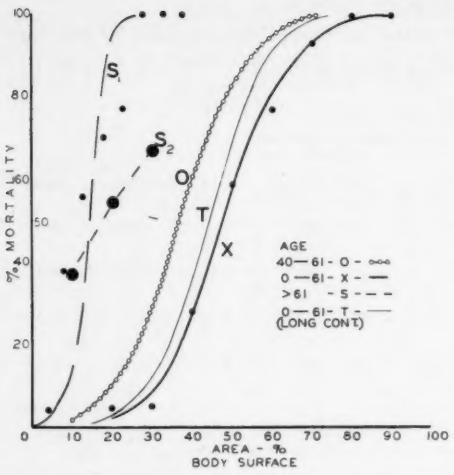

Fig. 1. Dosage-mortality curves of thermal injury derived with the use of probits from data collected in Dallas, Texas, between 1944 and 1951. The agreement of the fitted curves S_1 and X with the plots of actual data (small closed circles) is shown.

Curve marked S_1 obtains for persons having passed their 61st birthdate; that marked O for individuals between their 40th and 61st; that designated X applies to persons 0 to 61 years old who suffered thermal injuries of both long and short contact types; and the one labelled T pertains to ages 0 to 61 who suffered long contact injuries only. (See text for explanation of long and short contact designations and the significance of dashed curve S_2).

TABLE 4
χ^2 ANALYSIS OF SLOPE VARIANCE

$$\chi_b^2 = \frac{(b_1 - b_2)^2}{\frac{1}{[wx^2]} + \frac{1}{[wx^2]}}$$

Dallas Series 0 — 15 year = A
Dallas Series 2 — 15 year = B
Dallas Series 15 — 61 year = C
Dallas Series 0 — 61 year = D
Dallas Series 61+ years = E

A:B, χ^2_b =	.33,	P =	> .5	
A:C, χ^2_b =	.1,	P =	> .7	
A:D, χ^2_b =	1.5,	P =	> .2	
A:E, χ^2_b =	8.28,	P =	< .01	$\chi^2_{.01}$ = 6.635
C:E, χ^2_b =	10.6,	P =	.001	
D:E, χ^2_b =	28.88,	P =	< .001	

tion accounting for the difference between the slopes of the probit curves for the age groups 0 to 60, and the 61 years and older, is less then 0.001.

(χ_b^2 of D:E, table 4, Sec. I = 28.88) N = 1 Stating it differently: the larger increment in mortality per unit increment of area of injury obtaining in an aged "burn"-population, than in a young one, is related to the biologic characteristics of aging and not to chance. Toxicologically speaking, a burn is a more potent poison for an aged man than it is for a young one.

What are some possible causes of the aged individual's apparent incapacity to survive a burn? Because area estimation is the only criterion of severity of thermal injury employed in the analysis thus far, variance in depth of injury could be an important factor because the old individual is not as capable of exerting as violent avoidance reactions and consequently would tend to suffer deeper and, therefore, more lethal burns than the young person. The depth of injury among those dying before separation of the eschar cannot be adequately ascertained. Because the depth of injury is proportional to the length of time the organism is subjected to the heat, the only simple means of testing the depth factor is to divide the thermal injuries of the young group into 2 series; one designated as long contact[1] and the other as short contact[2], and then comparing the mortality curves of the long contact and aged groups. See Series V and VI, table 1, and compare the long contact mortality curve with that of age 61+ of figure 1 (Curves T and S_1 respectively).

Although the long contact curve T is slightly to the left of the curve X (L+ S)[3]

[1] Long contact injury—clothing fires, bed fires, conflagrations, falls upon hot objects, immersion scalds.

[2] Short contact—explosions of all types when unattended by iginition of clothing, spill-scalds.

[3] Long contact + short contact.

and the LD 50 is 44.07 instead of 49.16 (table 3) the long contact curve does not approach that of the aged population; in other words, variance in depth of injury accounts for very little of the discrepancy between the death-rates of the young and old burn-population if it accounts for any of it.

The second possibility is that the inherently more rapid rate of dying per unit time among the aged when superimposed upon the killing propensity of burning shifts the mortality curve of thermal injury to the left. A reasonable theoretic test of the influence of this possible factor can be effected by assuming that within the population parameter of the aged burn-population in Dallas (N = 42) and the time limits of hospitalization of this age group (3 hours to 244 days) that one-eighth, 5, of this population would die within the time limit without having been burned. Upon taking these 5 individuals from the dead aged burn-population and adding them to the living and distributing this correction as 3 to the 5 to 14 per cent and 2 to the 15 to 24 per cent surface area series of table 1, horizontal column 1, the raw-data plot[1] of the dosage-mortality relationship is moved slightly toward the dosage-mortality plot of the younger population, but not nearly enough to effect coincidence between their respective fiducial limits. Therefore, it is unlikely that the more rapid rate of dying inherent in an aged uninjured population accounts for the observed differences between the dosage-mortality curves of the young and old after burns and scalds.

Non-comparability of the burn-area distributions of the aged and young burn-populations is another extraneous factor that could affect the positions of the dose-mortality curves to some extent. The frequency distributions of burn-areas of the young and old populations are homogeneous (table 1). Therefore, non-comparability of burn-area distributions cannot be an important cause of the difference between the lethalities of thermal injury among the old and the young.

[1] S_3 of figure 1.

Thus, it seems that the difference existing between the death-rates attendant upon thermal injury among the old and the young is largely due to a difference between their biologic capacities to withstand burns and scalds.

Wherein does this difference lie—between their capacities to withstand shock, malnutrition, or infection?

Upon plotting the rates of dying of the dead-burn populations above and below the age of 61 years evidence is accrued indicating that variance in the rate of dying during the first twenty-four to forty-eight hours after the injury likely accounts for some of the difference between the mortality curves of the young and the old (fig. 2). Twenty-four hours after injury the difference in per cent of living between the young and the old, who ultimately die of injuries covering 60 to 75 per cent of their body surface, is 40. This difference is maintained until the tenth day when all the aged individuals are dead. The practical coincidence of the 60 to 75 per cent (ages 61+) and 75 to 100 per cent (ages less than 61) curves is interesting and suggests that the rate of dying of the ultimately dead young and old burn-populations should coincide should the comparison be effected between physiologically comparable injuries. Figure 3 is an attempt at such a plot employing the straight sections of the dosage-mortality curves to delimit the population limits; (10 to 30 per cent body surface injuries for the ages 61 and over, and 30 to 60 per cent body surface injuries for ages less than 61). The rate of dying of those who die after physiologically or toxicologically comparable injuries is roughly the same above and below the age of 61 years.

The fact that the aged who die after burns die more rapidly than the young after topographically similar injuries, largely because of the far more rapid rate of dying during the first twenty-four to forty-eight hours after injury, indicates that the difference between the positions of the ultimate mortality curves of the aged and the young is very likely due in part to the aged individual's relative in-

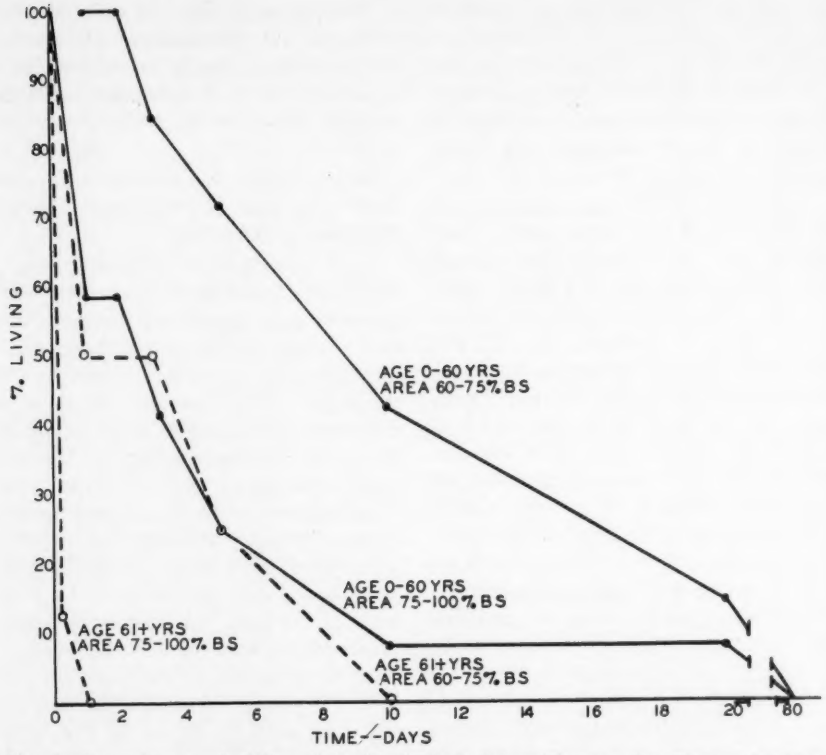

Fig. 2. Percentage survival-time plots of individuals dying of burns and scalds covering 60 to 75 per cent and 75 to 100 per cent of the body surface. The populational parameter, 0 to 61 years, is designated by continuous lines and the aged, over 60 years, by the discontinuous ones.

capacity to withstand the acute changes in his internal physiologic environment immediately attendant upon the injury or his failure to respond favorably to the therapeutic measures found to be efficacious among the young. Therefore, there is hope of materially reducing the mortality attending thermal injury among the aged by investigating the peculiarities of traumatic peripheral circulatory failure among aged animals and old men and women.

No information is available pertaining to the relationship of aging to the capacity of the individual to adjust to the nutritional, bacterial, and other physiologic derangements attending thermal trauma.

The capacity of withstanding thermal injury is seemingly not maximal at birth. There is some indication from the Dallas data, although too scanty to permit probit analysis, that it increases from birth to the age of 2 years. By virtue of the close coincidence between the earlier British mortality-surface-area-age relationships with the American relationships, the 2 sets of data were combined in the age parameters 0 to 2nd, 2nd to 15th, 15th to 61st, and 61 + years of age and subjected to probit analysis. Section III of table 3 is a summary of these analyses. The LD 50 of individuals aged 0 to 2 years was distinctly less than that for persons between the 2nd and 15th years of life. Although this lends a little more support to the view that infants do not tolerate

thermal injury as well as older children, more experience must be had with burned infants in a single institution before this impression can be considered as fact. However, after the second birthday the capacity

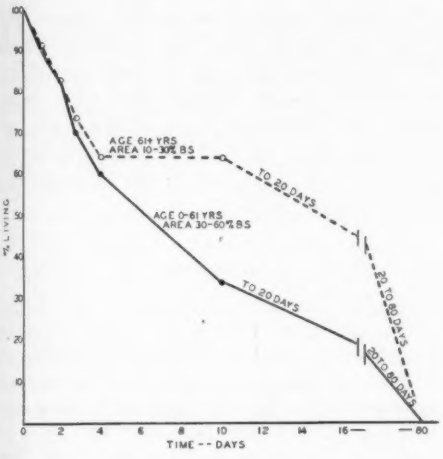

Fig. 3. Two percentage survival-time plots of persons dying of burns and scalds covering 10 to 30 per cent and 30 to 60 per cent of the body surface of individuals aged over 60 years and 0 to 61 years, respectively.

to live after being burned or scalded remains steady until the last part of the third or first part of the fourth decade (25 to 35 years) when it starts to decline. The rate of decline of the capacity to withstand thermal trauma between the 20th and 80th year of life closely approximates the curve $y = -2.2X^2 + 4X$.[1] The solid line of figure 4 is the plot of (y)LD $50 = -2.2X^2 + 4X$ between the age limits of 20 to 80 years; age 20 = decade 0, age 80 = decade 6.

The large closed circles are the LD 50's of the American age groups 2 to 15 years, 40 to 60 years, 60 to 80 years. The age curve of LD 50 was determined using the Dallas data and graphic analysis. After the curve was plotted, the LD 50's for five year intervals were taken from Bull and Squire's table 3 and plotted as the small open circles; *the coincidence is remarkable.* The degree of coincidence between the plots of the British and American experience forces me to retract

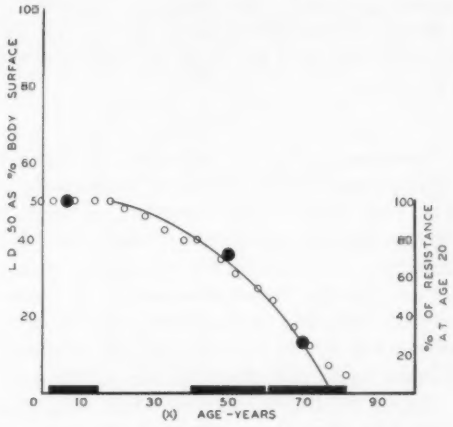

Fig. 4. Resistance to thermal injury relative to age of the individual. The L.D. 50_s of thermal injury in terms of per cent of L.D. 50 at age 20 were employed as measures of resistance. The large solid circles and the fitted line were derived from the Dallas data; the small open circles were taken from table 3 published by Bull and Squire (3).

a statement made over a year ago; to wit: "However, their (Bull and Squire's) mortality probability tables make undue allowance for age prior to age 60 and consequently death expectancies for adult series calculated with the use of their table tend, in our judgment, to be entirely too high." That statement is obviously false in the light of a more comprehensive analysis of the Dallas data.

Cognizance of the speed with which the death-rate attending a unit area of thermal injury increases with advancing years is requisite to the analysis of the effectiveness of burn-therapy in all institutions. If it is not, false impressions regarding the relative merits of therapeutic regimens could readily be gained should the raw-mortality statistics from a children's hospital be compared with the raw-statistic drawn from a hospital in

[1] y = capacity to withstand thermal injury expressed as LD 50's with LD 50 at age 20 taken as 100 per cent (LD 50 at age 20 = 49.16 per cent body surface injury—graphed as 50 per cent in figure 4).
X = units of age between the limits of 20 and 80 years: age 30 = age interval 1, age 80 = age interval 6.

which the aged are treated. Bull and Squire (3) have constructed a mortality-probability nomogram based on the relationship of burn-mortality to the extent of injury and the age of the injured person. The use of their nomogram permits an easy, rapid, and accurate analysis of the thermal-injury-death-rate within an institution regardless of the age parameters of the burn-population cared for within it.

Summary

Aging reduces one's capacity to withstand injury at an exponential rate after the 25th to 30th year of life. This process is related to the biologic characteristics inherent in aging and not to extraneous factors such as sampling-error (non-comparability of burn-area distributions of the young and the old), variance in depth of injury, and the inherently more rapid rate of dying among the aged.

Shock attendant upon thermal injury is more refractory to treatment among the aged than among the young.

After topographically similar burns and scalds, the young who die die more slowly than the aged. However, when cognizance is taken of the relative incapacity of the aged to withstand thermal injury and the rate of dying is determined after functionally similar burns the aged who die are found to die *no more* rapidly than the young who do.

Material improvement in the treatment of old burned people could, in all likelihood, be effected should we learn to treat peripheral circulatory failure among the aged more effectively. The treatment of the aged person suffering burn-shock is still a relatively unsolved problem, albeit in the treatment of burned youth it is not.

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PREDICTING SCIENTIFIC PRODUCTIVITY IN LATER MATURITY FROM RECORDS OF EARLIER DECADES

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WHEN a scientist is considered for appointment to a position or for promotion, attention is usually given to his publication record. This seems to imply that the scientific contributions which he has produced in the past are indicative of future performances in this regard. But, so far as we are aware, no test of this assumption has been made. In this communication we present certain data concerning this hypothesis. The data are derived from 2 groups of scientists chosen primarily because their bibliographies were conveniently available. In order to be able to analyze data pertaining to a considerable part of the life span, we chose for study only persons who had reached or exceeded age 70. As an index of productivity, the number of publications has been used.

GROUP I

Murchison in 1932 published the *Psychological Register*, Vol. III, a volume which undertook to list the world's living psychologists of that time, together with certain biographic data and a complete bibliography for each person. We have chosen for study the 43 men listed by Murchison who were born between 1850 and 1860. The number of bibliographic items per decade up to age 70 was determined for each subject.

For the most part, psychologists of this time period were Europeans. In our group of 43, Germany, France, and Great Britain have 7 men each; 15 more are distributed among 11 other European countries; the remaining 7 are Americans.

Members of this group varied greatly in their productivity. By age 70, Havelock Ellis, the most productive, had 240 publications. Freud, who was second, had 201, and Zwaardemaker was third with 162. At the other end of the distribution were 2 persons with 1 publication each and 2 others with 2 each. The distribution of productivity resembles closely that of other groups of psychologists (1) and of scientists generally (2).

The product-moment correlations between decades are shown in table 1. It will be noted

TABLE 1

CORRELATIONS BETWEEN SCIENTIFIC PRODUCTIVITY IN DIFFERENT DECADES OF LIFE FOR GROUP I. Figures in Table Indicate r Values

Decade	30–39	40–49	50–59	60–69
20–29	.58	.31	.51	.53
30–39		.80	.73	.68
40–49			.71	.65
50–59				.82

Additional r's:

r (20–29)	(30–69)	.54
r (20–39)	(40–69)	.81
r (20–49)	(50–69)	.77
r (20–59)	(60–69)	.82

that, aside from the correlations between the 20's and the 30's, the r's between adjacent decades have values between .71 and .82. Correlations between non-adjacent decades are slightly lower, but productivity in the 60's is related to the extent of .68 and .65 to productivity in the 30's and 40's, respectively. In general, the 20's provide the poorest basis of prediction. Probably this is partly because publication seldom begins before the late 20's, and for that reason the samples of

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productivity obtained from the 20's are small ones. Although the 20's give the lowest correlations, it should be noted that the r between the 20's and the 60's is .53, a high value for periods separated by 30 years.

In addition to the relationship mentioned previously, table 1 also shows the correlations obtained when the period between age 20 and age 70 is divided into two segments, using various points as the place of division. In general, this treatment of the data does not increase the obtained correlations. Productivity in the 60's, for example, can be predicted as well from the record of the 50's alone as it can be predicted from the entire record from 20 to 60.

Group II

This group consisted of recently deceased members of the National Academy of Sciences. Following the death of a member, this society publishes a biographic account and bibliography in the *Biographical Memoirs* of the society. We chose subjects from the volumes of the *Memoirs* published between 1943 and 1952, inclusive. From this list we selected only persons who lived to age 70 or beyond, and whose bibliographies in the *Memoirs* comprised complete rather than selected lists of publications. Persons whose contributions to science consisted chiefly of patents were excluded from our group, since we wished to limit our analysis to publications. Psychologists were also excluded, since we wished to avoid overlapping between Groups I and II. Our final list contained 41 names.

In this group, the average productivity was much greater than in Group I. The highest record of productivity in the National Academy group was made by a biochemist who had 765 publications. The smallest bibliography, containing 27 items, was that of a mathematician. It is likely that some scientific specialties lead to more prolific publication than do others. However, the members of any scientific group represented in the National Academy of Science show a great range of scores. For example, one biologist's bibliography had 600 items, another biologist's 36; one engineer published 362 items, another 48. Differences between scientific groups, therefore, account only in part for the consistency in publication rates which are to be reported.

In general, the correlations for Group II are very similar to those for Group I. Aside from the top row in table 2, the value of r for adjacent decades in other parts of the table varies only from .79 to .86. The third decade of life is again found to offer the poorest basis of prediction and is actually valueless as a predictor for the period from age 60 to age 70. However, productivity in this decade can be predicted surprisingly well on the basis of productivity in the 40's and 50's.

Table 2
Correlations Between Scientific Productivity in Different Decades of Life for Group II
Figures in Table Indicate r Values

Decade	30–39	40–49	50–59	60–69
20–29	.57	.48	.37	.09
30–39		.79	.78	.53
40–49			.86	.73
50–59				.86

Additional r's:

r (20–29)	(30–69)	.42
r (20–39)	(40–69)	.68
r (20–49)	(50–69)	.74
r (20–59)	(60–69)	.70

Age Trends

Supplementary findings of some interest are shown in table 3, which shows the average

Table 3
Average Number of Publications per Person per Decade

Decade	20's	30's	40's	50's	60's
Group I	1.5	7.4	11.4	11.7	11.7
Group II	15.0	48.4	47.1	47.3	37.6

number of publications per person per decade. It indicates, as was noted earlier, that members of the National Academy of Sciences published more in all decades than our group of psychologists. This difference in productivity is to be expected since the psychologists were an unselected group of psychologists whereas the National Academy membership is very highly selected from among scientists in general.

As noted earlier, the decade of the 20's is the period of lowest productivity for both groups. Group I reaches its maximum productivity in the 40's, Group II in the 30's. The psychologists maintain the level reached in the 40's until age 70. The eminent scientists maintain their extraordinarily high record for 3 decades, but drop somewhat in the 60's.

Readers who are acquainted with Lehman's data (3) may be surprised at the figures presented above, since most of Lehman's figures show a sharp drop in productivity after age 50. However, the majority of the data compiled by Lehman refer only to outstanding works, whereas our data refer to total publications. It would seem that there is a marked difference between the age trends for works of greatest value and age trends in total works.

The persistence of scientific activity on the part of members of the National Academy merits further comment. Examination of individual records shows that the high averages for the sixth and seventh decades shown in table 3 are not due to the exceptional records of a few individuals. Every member of this group published something both in his 50's and in his 60's. In either decade, only 10 men produced fewer than 10 papers each; all others produced more. The top record for the decade of the 60's was a bibliography of 226 items, or more than 22 per year for these 10 years. This record was made by the biochemist who achieved the highest total record of productivity.

Summary and Discussion

The data which have been presented show that scientists' productivity in their 60's can be predicted with fair accuracy from their productivity in earlier periods. The men who have been productive earlier in most cases continue to contribute at least until age 70.

The consistency of scientific activity just described holds throughout the age span which was studied. In general, it was found that for the period of 30 to 70 years, the number of publications published in adjacent decades correlated in the neighborhood of .80. Non-adjacent decades showed sizeable but somewhat lower relationships. The period between age 20 and age 30 provided the poorest basis for predicting later achievement.

In the field of prediction, correlations as high as those which we have obtained are quite rare. However, we are not aware that records of scientific publication have previously been submitted to this type of analysis. Our results suggest that correlating the productivity of different decades may profitably be extended to other groups, to other types of creative endeavor, and to the period beyond age 70.

Attention is also called to the fact that the scientists in our groups showed little decline in rate of publication up to age 70, the point at which the study was terminated.

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WORK AND RETIREMENT FOR OLDER UNIVERSITY ALUMNI

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(From The Pennsylvania State University, State College, Pennsylvania)

UNDERLYING the increasing scientific interest in older people are two facts: the increasing proportion of the population that is composed of old people and the loss of a positive, useful position for the majority of old people in our society. Investigations of the personal adjustment of older people have revealed that engagement in some form of gainful employment is a significant factor of good adjustment in old age, especially for men. This paper, one of the investigations of the Committee for Study of Adulthood, The Pennsylvania State University, reports the findings of a research project (1) concerning attitudes and opinions about work and the significance of retirement to 627 men, all alumni of The Pennsylvania State University.

A questionnaire, *A Study of Work and Retirement*, was mailed to each of the 1,757 men on the rolls of the alumni association from the class of 1866 through the class of 1913. Two and one-third per cent had died or their letters returned unclaimed; respondents totaled 627, or 36.6 per cent of the adjusted mailing list of 1,716. By statistical comparisons using information available in the alumni records, we determined the representativeness of the responding sample. Comparisons on attitudes and opinions were made between those who were retired and those who were not retired and conclusions are drawn regarding differences between these groups.

In order to determine how well our respondents represented the total study group, respondents and non-respondents were compared by means of the chi-square. This statistical procedure enables us to compare the results we obtained with those to be expected on the basis of chance alone. In this way we discovered that our responding sample—about one-third of the total list—was biased to a significant extent in these ways: it contained *more* than to be expected of graduates of the University (an undersampling, then, of those who left the University without graduating), slightly *more* than we would expect of those who graduated from the University *before* 1908 (presumably, then, a few more than to be expected of those of about the usual retirement age), and *more* than to be expected of those living outside Pennsylvania. When respondents and non-respondents were compared on the basis of their curricular pursuits, no statistically significant differences were revealed. Similar investigations have shown that, in part, our sample biases are what might have been predicted, since respondents to such surveys are usually those persons who are especially interested in the topic or who are loyal to the institution sponsoring the survey (2). It is important to keep in mind these preliminary facts concerning this study population.

Table 1 shows some additional facts concerning our respondents, facts obtained from them concerning age, graduating class, attendance at alumni meetings, and retirement. As shown there, about 1 in 9 of our respondents attend their alumni organization meetings regularly, slightly less than one-half attending only occasionally, with 41.8 per cent never attending. In response to the question "Are you retired?," 410 men, about two-thirds, answered no. Two hundred seventeen men answered in the affirmative, and of these, three-fourths had retired since World War II. Men still working were holding positions (not unlike those formerly

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TABLE 1. NUMBER AND PERCENTAGE OF 627 MALE UNIVERSITY ALUMNI HAVING CERTAIN CHARACTERISTICS

Characteristic	Number	Percentage
Age 55—64	286	46.0
Age 65—90	336	54.0
Graduating class before 1910[1]	303	49.0
Graduating class 1910—1913[1]	316	51.0
Attend alumni meetings regularly	65	11.2
Attend alumni meetings occasionally	273	47.0
Attend alumni meetings never[2]	243	41.8
Retired (median age = 69.1)	217	34.6
Retired before 1945	44	21.4
Retired 1945—1951	160	78.6
Non-retired (median age = 63.6)	410	65.4

[1] Includes non-graduates who left school during these years.
[2] Includes some in whose locales there were no organized groups of alumni.

held by the men already retired) as engineers, teachers, lawyers, farm operators, sales personnel, physicians, and forestry and horticulture specialists. Many were and are self-employed. Later comparisons in this paper deal with two groups of men: the retired (median age 69.1) and the non-retired (median age 63.6). These results are summarized in tables 2, 3, and 4.

It will be observed from table 2 that in many ways the retired men are very similar to the non-retired men. Many of the percentages are almost identical. For example, on item 2, almost identical percentages of the retired and the non-retired answered "yes" to the question, "Do you feel your present source of income gives you permanent security?" Those percentages that are different to the extent to which we can say that the difference could not have happened simply by chance are marked by asterisks. On the question concerning gainful employment, the differences between the two groups are, of course, statistically significant and are marked accordingly. Two-thirds of the retirees were not working for money at all, and two-thirds of these were not interested in such work. A considerable number did not feel physically able.

"What meaning has work had in your life?" This question, with several alternatives for checking if they applied, was included in the inquiry and results are shown also in table 2. The retired and non-retired men did not differ appreciably; about the same proportion of each group believed their work had given them self-respect and the respect of others. Virtually all of both groups considered that their work had brought satisfaction and enjoyment (item 6). The results of these comparisons show little difference in the ways that retired and non-retired alumni from the University regard work.

When the men were asked what things about their jobs they thought they would miss when retired, or that they had missed when they did retire, three real differences of opinion were evident. As shown in table 2, three-fifths of the retired group said they missed friends they had made on the job, while only one-half of those yet to retire thought they would miss such friends. More of the non-retired men than expected by chance believed they would miss the income, 57.3 per cent indicating thusly; nearly 20 per cent less, 39.7 per cent, of those already retired considered that income was something

TABLE 2. CHARACTERISTICS AND OPINIONS CONCERNING WORK HELD BY 627 MALE UNIVERSITY ALUMNI, RETIRED AND NON-RETIRED, BY PERCENTAGE

Characteristic or Opinion	Retired N = 217[1]	Non-Retired N = 410[1]
1. Self-rating on health "good" or "excellent"	70.4	80.9
2. Present source of income gives permanent security	70.8	68.4
3. Gainfully employed now		
Full-time	10.1*	95.2*
Part-time	21.6*	4.8*
None	68.3	
4. Retired: If not working, why not? (N = 131)		
Physically unable	18.3	
Unable to secure any position	3.1	
Unable to secure position desired	11.5	
Not interested in employment	67.1	
5. What meaning has work had in your life?		
Self respect	58.6	61.9
Respect of others	50.2	53.0
Chance to be with and work with other people	59.6	54.5
Way of earning a living	70.8	73.7
Chance to be creative	54.8	52.1
Source of new experiences	46.0	44.3
Filled my day and gave me something to do	30.0	30.3
6. Work has brought satisfaction and enjoyment	98.0	97.0
7. What things do you think you will miss (did miss) about your job when you retired?		
Being with other people	38.6	35.4
Friends I've made on the job	60.2*	59.4*
Income	39.7*	57.3*
Sense of satisfaction in a job well done	59.3	56.6
Routine	14.7	13.4
Sense of being creative	33.3	31.5
New and interesting experiences	39.2	35.7
Self-respect I get from the job	34.3*	43.0*
Recognition from other people	28.9	30.2

[1] On individual questions N varied, depending on the number of persons answering the question. On several items, e.g., No. 5, most respondents checked more than one response: percentages are of the total number of persons answering the question.

* Statistically significant differences between retired and non-retired groups at the 5 or less than 5 per cent levels.

they did miss. It would seem that the non-retired men were more apprehensive about the economics of retirement, while the retirees were more concerned with the social aspects of retirement. There was a significant difference, too, between the groups on the missing of self-respect they obtained from working, about one-third of the retirees mentioning that factor as compared with 43 per cent of the non-retired men.

Item 1, table 3, shows that among the non-retired men there is a considerable proportion who have thought little about retirement. Some said they did not intend to retire at any time. Three out of 4 of them were making some financial arrangements, however,

with almost one-half working at present on activities they said they could continue into retirement (item 2).

The alumni were asked their opinions about certain alternative schemes of retirement. The question was raised, first of all, as to whether or not there should be an established age, preferably the same age, for retirement from most occupations. Significantly more than expected of the retirees (30.6 per cent) said there should be an established age for retirement, with only 22.6 per cent of the non-retired men believing so. Apparently many of those already retired believed all people should abide by the uniform regulation of compulsory retirement because of age. About the same proportion of each group were in favor of a half-time workload plan after 60 years; this was true, also, of the flexible plan which would permit retirement any time between 60 and 70 but which also required periodic medical and psychologic examinations. As seen in table 3, item 5, large proportions of both groups were in favor of this plan; many men commented, however, about the practical administrative difficulties they could forsee.

Should men and women have the same rules and age for retirement? Many respondents said they should, but many believed it really should depend on individual capabilities, not on sex. Others said flatly that women should retire about five years earlier. However, one man commented succintly, "Women live longer; they ought to work longer." Some refused to give an opinion; "I've had two wives and two mothers-in-law," one 77-year old said, "And experience has taught me never to express such an opinion."

Item 7, table 3, shows the proportion of retired and non-retired men expressing positive opinions on alternative choices of things they would like to do (or have done) when they reach 65. In regard to giving up work even with only a small income, small percentages, but significantly more of the retirees (17.9 per cent) than non-retirees (9.1 per cent), checked this alternative. Significantly more of the non-retired alumni thought they would choose to continue working full-time on their jobs as long as they were able or else to continue working part-time in their special fields. Again, significantly more of the retired group (42.3 per cent, as compared with 22.5 per cent of the non-retired) thought a person should retire at an established age, here set at 65 (item 8). Considerable proportions of both groups believed retirement should come when a person's health suffered by working or when the individual had some useful activity to take the place of work. In item 9, table 3, respondents were asked if they were an employer would they employ a person over 65 if he were qualified? About 7 of 10 from both groups indicated that they would. Many individuals qualified their answers, however, with the reference being made to the financial risks involved; some of the men remarked about the added advantages of the lowered rates of absenteeism and of the wisdom often coming with older workers.

The proportions in item 1, table 4, reveal some significant differences between the two groups on certain opinions about retirement. More of the retirees than we would expect by chance considered that retirement brought welcome relief from responsibilities and that it was a reward for a lifetime of work. Significantly few of those already retired believed that retirement was only for those physically unable to work or that retirement took the meaning out of life. In contrast, of those who have yet to retire, almost one-half thought it was only for those physically unable and one-fifth believed retirement simply took the meaning out of life. "I'm never going to retire," some of them said. "I'd rather die on the job."

No appreciable differences were apparent between the two groups about the things with which they were concerned in connection with retirement. As seen in table 4, item 2, more than 50 per cent were concerned with all of the items; those yet to retire anticipated the same concerns.

When asked how they felt about retirement, about 1 in 3 of the retired group be-

TABLE 3. CHARACTERISTICS AND OPINIONS CONCERNING RETIREMENT AND RETIREMENT PLANS HELD BY 627 MALE UNIVERSITY ALUMNI, RETIRED AND NON-RETIRED, BY PERCENTAGE

Characteristic Attribute or Opinion	Retired N = 217[1]	Non-Retired N = 410[1]
1. *Non-retired:* Have you thought about retirement?		
Not very much		28.7
Some		32.6
A great deal		38.7
2. *Non-retired:* What are you doing to prepare for retirement?		
Making financial savings arrangements		72.3
Planning a new business or practice		13.9
Working on activities I could continue into retirement		47.3
3. For retirement from most occupations, there should be an established age, preferably the same age	30.6*	22.6*
4. There should be a plan which would permit an employee to reduce work-load to half-time after 60 and which would give corresponding reduction in salary	69.4	68.1
5. There should be a flexible retirement plan which would permit employees to retire any time between 60 and 70, but which would also require them to take periodic medical and psychologic examinations to determine whether or not they should retire	88.4	84.0
6. Men and women employees should have same rules and age for retirement	52.7	57.0
7. If you were given your choice, what would you do (have done) when you reach 65?		
Give up working even though I have only a small income	17.9*	9.1*
Give up working only if I had enough to live on comfortably	44.4	40.6
Continue working full-time on my job as long as I'm able	44.8*	58.8*
Continue working full-time even if I had to do something else	17.0	21.2
Continue working part-time in my own field	51.5*	62 5*
Continue working part-time on some other job	31.1	31.6
8. When do you think a person should retire?		
At 65	42.3*	22.5*
At 70 or older	21.8	16.6
When his health suffers by working	56.4*	65.2*
When he can afford it	39.3	36.8
When he is no longer able to do his job well	49.7	54.6
When his job is no longer interesting to him	26.6	32.7
When he has some useful activity to take the place of work	53.0	47.3
9. If you were an employer or in charge of employment policies of a business, factory, or school, you would be willing to hire a new employee past the age of 65 provided he had the same qualifications as other younger applicants	69.4	72.0

[1] N varies somewhat with individual questions.
* Statistically significant differences between retired and non-retired groups at the 5 or less than 5 per cent levels.

TABLE 4. OPINIONS CONCERNING RETIREMENT HELD BY 627 MALE UNIVERSITY ALUMNI, RETIRED AND NON-RETIRED BY PERCENTAGE

Opinion	Retired N = 217[1]	Non-Retired N = 410[1]
1. Opinions about retirement		
It lets you do things you never had a chance to do before	52.3	52.2
It is a welcome relief from the responsibilities and obligations of younger days	42.0*	32.0*
It's a reward for a lifetime of work	44.7*	38.4*
It's only for people who are physically unable to do their jobs	15.7*	47.5*
It gives younger men a chance to get a job	38.1*	30.4*
It takes the meaning out of life	11.9*	20.4*
It's the expected thing for older people to do	30.9	31.2
2. Which things are you concerned about in connection with retirement?		
Keeping up my standard of living	50.5	46.7
Being able to take care of myself	59.8	51.6
Still being a part of things going on in the world	55.3	61.4
Finding interesting things to do	50.5	52.0
Still being of use to those about me	66.6	59.2
Nothing	5.4	3.8
3. Feelings about retirement		
A well-earned rest	32.0*	21.2*
The worst thing that can happen to a person	13 3*	31.0*
An acceptable thing for older people	45.0	43.1
4. Still making a significant contribution to society	74.8*	96.5*

[1] N varies somewhat with individual questions.
* Statistically significant differences between retired and non-retired groups at the 5 or less than 5 per cent levels.

lieved it was a well-earned rest, significantly greater than the 1 in 5 of the non-retired men who believed likewise. In fact, one of three non-retired alumni thought retirement was the worst thing that could happen to a person, while only 1 in 8 of the retired group believed this way.

"Do you think you are still making a significant contribution to society?" In reply to this question almost all of those not yet retired (96.5 per cent) thought that they were; significantly fewer, but still three-fourths of the retirees (74.8 per cent), answered this question positively. One of 4 retired alumni answered in the negative. These feelings are substantiated by feelings of usefulness, as expressed on a section from the Attitude Inventory of the schedule, *Your Activities and Attitudes* (3, 4). Significantly few retirees were in the uppermost score categories on usefulness, as compared with the non-retired men. A coefficient of contingency, corrected, was calculated to determine the extent to which feelings of usefulness go with retirement; the result was a C_{cor} value of .56, the probability of this being a chance occurrence of 1 in 100. Similarly, happiness scores, also derived from *Your Activities and Attitudes*, were compared, a statistically significant coefficient of contingency of .20 the result. There was a *slight* tendency for those not yet retired to be happier than the retirees.

The difference between the non-retired and retired university alumni whose attitudes and opinions are compared here cannot be said to be the result of work *per se*. Happiness and satisfaction throughout all the years of life require adjustment to many intricate personal and social problems. Complicating the picture of retirement are other

adjustment problems of advanced age—the loss of one's long-time friends, one's spouse, decreased income, less physical vigor. To retire from work, however, would seem to make these more difficult when the worker believes that personal morale depends upon gainful employment. The negative feelings about retirement were expressed in the frequent comment of the self-employed non-retired respondent in our study: "I *never* intend to retire." Engagement in work, then, seems to be a symbol to many of value, of worth; to them retirement must come to mean being dependent and decrepit, lonely, unemployable, and unwanted, hence without worth.

In a technologic society, aging as rapidly as our own, we cannot afford to see retirement this way. There must be a social philosophy which will allow man to grow old, to retire from work, and to die, without disgrace and demoralization. There must be, too, sound, adequate social and psychologic as well as financial preparation for the years which can be the culmination of a useful, happy life.

Retirement with its negative associations is not an inevitability. Many of the retired university alumni in this investigation enthusiastically refute this notion. To the self-employed, retirement is undoubtedly a different story than to those workers who have little control over their own retirement. Study of the voluntary retirement of the self-employed individuals in several social and economic and occupational classifications could be of significant value in understanding this phenomenon.

Summary

This investigation has compared attitudes and opinions of 627 men who were retired and non-retired university alumni, and who had returned questionnaires concerning work and retirement. By statistical comparisons, we determined that the responding sample is not entirely representative of the total group.

About two-thirds of the respondents were not retired at the time of the survey. Their median age was 63.6 while for those already retired it was 69.1. Work had apparently meant about the same to these two groups. Comparative analyses of opinions concerning retirement revealed that non-retired men apparently were more apprehensive about the finances of retirement, while the retirees were more concerned with personal and social aspects of retirement.

The alumni were also asked their opinions about certain alternative plans of retirement. The two groups held the same opinions on several schemes, but significantly more than expected (still only one-third) of the retirees said there should be an established age for retirement.

Comparisons were made between the two groups concerning their opinions about what to do at 65 or when a person should retire. In general they reveal that those still working resist the idea of retirement, that it should come only when absolutely necessary. Nearly one-half of them said it was only for those physically unable to work; indeed, one-third felt that retirement was the "worst thing that could happen to a person." While not all of those already retired expressed opposite opinions, it would seem that the retirees see the brighter side of the experience, perhaps by psychologic necessity, since there would be little opportunity to change the situation. In a technologic society aging as rapidly as our own there must be a social philosophy which will allow man to grow old, to retire from work with grace and with favor; unless we provide work to the last, we cannot afford it otherwise.

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Program of the Seventh Annual Scientific Meeting of the Gerontological Society, Inc. in Cooperation with the Fifth Annual Southern Conference of the Institute of Gerontology of the University of Florida

UNIVERSITY OF FLORIDA, GAINESVILLE, FLORIDA

E. L. BORTZ, *Chairman*, Program Committee

R. W. KLEEMEIER, *Chairman*, Local Arrangements Committee

TUESDAY, DECEMBER 28, 1954

8:30-9:30 a. m. Registration, Broward Hall, fee $1.50.

(For program of the Section on Biological Sciences, see July issue, pages 359-364)

12:30-1:45 p. m. Luncheon Meetings, Broward Hall, $1.25 per plate

SECTION ON BIOLOGICAL SCIENCES

SECTION ON PSYCHOLOGICAL AND SOCIAL SCIENCES

WEDNESDAY, DECEMBER 29, 1954

Morning Session, 9:30 a. m. - 12:00 noon

Section on Psychological and Social Sciences, Walker Hall Auditorium.

J. E. BIRREN, *Program Chairman*

Psychologic and Psychophysiologic Measurement in the Aging.

Chairman: S. L. PRESSEY, Ohio State University
Columbus, Ohio

REITAN, R. M.—The Distribution According to Age of Psychologic Measures Dependent Upon Organic Brain Functions.

McFARLAND, R. A., and FISHER, M. B.—Alterations in Dark Adaptation as a Function of Age.

DEMMING, J.—Tests "Indigenous" to the Adult and Older Years.

KLEEMEIER, R. W., and JUSTISS, W. A.—A Hearing Aid Program in a Community of Aged Persons.

Retirement and Community Programs for the Aging.

Chairman: R. A. McFARLAND, Harvard School of Public Health,
Boston, Massachusetts

PRESSEY, S. L.—Problems and Potentials of Professional Retirement.

HUNTER, W. W., and MAURICE, HELEN—Community Action for the Aging.

SALAMONE, A.—The Role of Adult Education Administrators in Organizing Programs for Senior Citizens.

Section on Clinical Medicine, Broward Hall

W. B. KOUNTZ, *Program Chairman*

Chairman: T. C. CASSON, Jacksonville, Florida

ABBOTT, OUIDA, D.—Blood Studies of the Aged.

KLEH, J., and FAZEKAS, J. F.—The Effects of Hypotensive Agents on Patients with Cerebral Vascular Insufficiency.

SWARTZ, F. C.—Medical Responsibility for the Older Patient.

ACKERMANN, P. G., TORO, G., and KOUNTZ, W. B.—Serum Lipoproteins in Older Individuals.

HARRIS, R.—Results of Reserpine Therapy in Hypertension.

EDWARDS, J. E., BURNSIDES, C., SWARM, R., and LANSING, A. I.—Atherosclerosis in the Intramural as Compared to Extramural Coronary Arteries.

12:30 p. m. Luncheon Meeting, Council of the Gerontological Society, Inc., Broward Hall

Afternoon Session, 2:00 - 5:00 p. m.

Section on Clinical Medicine, Walker Hall Auditorium

Chairman: W. B. KOUNTZ, Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri

ALBANESE, A. A., HIGGONS, R. A., ORTO, LOUISE, and ROSSY, JOAN—Utilization and Protein Sparing Action of Carbohydrates in the Aged.

FERDERBER, M. B.—Physiologic Reserve in the Chronically Ill and Aging.

GLAZIER, F. W., and GOFMAN, J. W.—Lipoproteins, Aging, and Coronary Artery Disease.

KEARNS, J. E., and CROFT, J. D.—Radioactive Iodine in the Treatment of Cardiac Disease in the Elderly.

PEARSON, S., and McGAVACK, T. H.—The Effect of Age upon the Relative Gonadal and Adrenocortical Activity of the Male.

BISSELL, L. F., and OBRIST, W. D.—Electroencephalographic Findings in a Study of Aged Patients with Cardiac Disease.

EPSTEIN, F. H., and BOAS, E. P.—The Incidence of Atherosclerosis in a Random Sample of a Union Population.

Read by Title:

SAMUELS, S. S.—Management of Peripheral Arterial Disease in the Aged.

POMERANZE, J.—A New Antidepressant (M.R.D.-108) in Geriatrics.

CRISLER, G. R.—Intermittent Claudication Treated with Ultrafaradism.

CRAMPTON, C. W.—"Deaging," Some Principles and Methods.

AMATO, L. L.—The Practice of Geriatrics.

STRASSMANN, G., and ASEKOFF, M.—Incidence and Importance of Diseases of the Gastrointestinal Tract in Mentally Sick Patients over 60 Years Old.

STORCH, S.—The Ballistocardiogram in the Aged.

ZIFFREN, S. E., GOLDSTEIN, M. S., and BEYE, C. L.—Fractures of the Neck of the Femur in the Aged.

LABECKI, T. D., and BUSBY, C. L.—Dihydrogenated Ergot Derivatives in Cerebral Arteriosclerosis.

FRIEDFELD, L.—A Geriatric Clinic in a General Hospital.

6:30 p. m., Annual Dinner, Broward Hall, $3.75 per plate.

Presidential Address—A. J. CARLSON, University of Chicago, Chicago, Illinois

Evening Session, 8:00 to 9:30 p. m.

General Meeting: **Recent Advances in Medical Handling of the Geriatric Patient**
Walker Hall Auditorium

Chairman: T. Z. CASON, University of Florida, Jacksonville, Florida

Panel: N. M. MARR
C. O. ANDERSON
R. REESER
(Remainder of Panel to be announced later)

THURSDAY, DECEMBER 30, 1954

Morning Session, 9:30 a. m. - 12:00 noon

Section on Social Work and Administration, Walker Hall Auditorium.

J. WEIL, *Program Chairman*

Symposium: Social Work and Aging.
Chairman: C. TIBBITTS, Department of Health, Education, and Welfare, Washington, D. C.

Panel:

RANDALL, OLLIE A.—(Community Services Society, Inc., New York, New York). How Should Community Social Agencies Adopt Their Programs to an Aging Population?

KUPLAN, L.—(Governor's Interdepartmental Committee on Aging, Sacramento, California). How Can State and Local Agencies Integrate Their Services Better to Meet the Needs of Older People?

DONAHUE, WILMA T.—(Division of Gerontology, University of Michigan, Ann Arbor, Michigan). How Can Education Help Social Work and Administration Meet the Problems of Aging?

WAGNER, MARGARET W.—(Benjamin Rose Institute, Cleveland, Ohio). What Is the Role of Social Services in Aging?

WEBBER, I. L.—(Department of Sociology, University of Florida, Gainesville, Florida). What Are the Implications of Current Research in Aging for Social Work and Administration?

Contributed Papers:

SELLING, L. S.—(Orlando, Florida). Problems of Elderly Persons Without Family Ties.

MULVEY, MRS. G. F.—(Rhode Island Governor's Committee on Aging, Providence, Rhode Island). Administration of a Program on a Statewide Basis.

12:30 - 1:45 p. m., Luncheon Meetings, Broward Hall, $1.25 per plate.

SECTION ON CLINICAL MEDICINE. Address by E. HENDERSON—(Bloomfield, New Jersey). Endocrine Balance in Older People.

SECTION ON SOCIAL WORK AND ADMINISTRATION. Address by W. B. KISSINGER. Administration of Hospital and Home for the Aged

2:00 - 3:00 p. m., Business Meeting of the Gerontological Society, Inc., Walker Hall Auditorium.

Chairman: A. J. CARLSON, University of Chicago
Chicago, Illinois

Afternoon Session, 3:00 - 5:00 p. m.

Section on Psychological and Social Sciences, Walker Hall Auditorium.

J. E. BIRREN, *Program Chairman*

Symposium: Later Maturity and Employment

Chairman: Mrs. Georgia F. McCoy, Department of Health, Education, and Welfare, Washington, D. C.

Panel:

FERDERBER, M. B.—(University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania). Physical and Psychologic Aspects of Aging and Employment of the Mature Worker.

DANIELS, L. A.—(Florida State Employment Service, Tallahassee, Florida). The Role of the Community in the Development of Employment Opportunities for Mature Workers.

HAVIGHURST, R. J.—(University of Chicago, Chicago, Illinois). Education: the Role of Education in Helping the Mature Worker Maintain Occupational Skills and Develop New Skills.

BURNS, R.—(Industrial Relations Center, University of Chicago, Chicago, Illinois). Business and Industry: The Responsibilities of Business and Industry in Providing Opportunities for Employment to Older Workers.

BECKMAN, R. O.—(Hialeah, Florida). The Point of View of the Mature Individual: A Critique.

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Abstracts of Scientific Papers

Section on Psychological and Social Sciences

Tests "Indigenous" to the Adult and Older Years.

J. DEMMING (*sponsored by S. L. Pressey*) *Ohio State University, Columbus, Ohio.*

The basic point of view of the project is that tests which are adequate to indicate the abilities of subjects in a given age group should be sufficiently part of its way of life, points of view, problems, and purposes that they seem natural and intrinsically interesting and appropriate; somewhat as tests for 10 year old children are made out of material appropriate to that age, so (it is hypothecated) tests for 40 or 60 year olds should be indigenous to those years.

Proceeding on this point of view, a variety of materials which are the especial concern of adults, and case reports of older people, were gone over, as well as literature on the characteristics of the adult and older years. It was hypothecated that maturity was distinctively characterized by a wide range of information regarding adult affairs, social perceptiveness, practical judgment, tendencies to be cautious rather than hasty or extreme in attitudes, and so on. Tests believed rather distinctive have been developed, which are thought of as having at least face validity in measuring such abilities.

These tests are being tried with a variety of groups including a grandmothers club, older veterans and penitentiary inmates, as well as students in adult evening classes and college and summer school students. Where possible, attitudes as to the appropriateness of the material, as well as test scores, are being obtained.

It is concluded that tests especially designed as appropriate to the adult and older years do show the older doing well and differentiate well between adults as to their competence.

Community Action for the Aging.

W. W. HUNTER and HELEN MAURICE, *Division of Gerontology, University of Michigan, Ann Arbor, Michigan.*

This report presents the findings of a two and one-half year project designed to bring about community action on behalf of older people living in a city of 175,000 population. The core of the project consisted of a number of adult education courses in gerontology in which elderly people enrolled and were given the opportunity 1) to achieve a better understanding of their own situations and those of their peers in the community and 2) to exercise a key role in the initiation of needed community change.

The second major aspect of the project involved the development of maximum community participation in obtaining information about the needs of older people as well as the extent to which the community was meeting these needs. Representatives from over 50 community groups and organizations worked with approximately 20 elderly students during the last year of the project and completed two comprehensive surveys: 1) a survey of the needs of a representative sample of the total population 65 years of age and older and 2) a survey of all existing programs, services, and facilities for the aging. The older people participated fully in each phase of the program including preparation and presentation of the final reports and recommendations to the community.

Newly created leadership among the aging, community-wide involvement in the programs, and a wealth of information about the aging from which to plan constituted the springboard for subsequent community action. Results of the project included the initiation of a number of on-going programs and the development of a community action committee for the aging to carry forward the development of additional programs and services.

Many communities are seeking ways to bring about changes which will enhance the well-being of their senior citizens. This project demonstrated methods for training older people for community leadership and for translating an adult education process into community action. It demonstrated also that older people possess marked potential for working constructively toward the solution of their own problems.

A Hearing Aid Program in a Community of Aged Persons.

R. W. KLEEMEIER and W. A. JUSTISS, *Moosehaven Research Laboratory, Orange Park, Florida.*

Hearing aids are supplied to hard of hearing residents in a fraternal home for the aged. More than 10 per cent of the 350 residents receive this service. Various aspects of the program will be described, including: (a) personal and social adjustment of the users; (b) problems encountered by the aged in using hearing aids; (c) types of hearing loss; and (d) cost of program.

Study of the more than 40 hearing aid users in this program indicates that as a group they are strongly attached to their instruments and tend to minimize their hearing loss.

When compared to others in the community, they tend more to project their personal inadequacies on others, lead more restricted lives socially, and suffer more from personal maladjustment.

Costs of the program may be analyzed in terms of the original cost of hearing aids, repairs, and batteries. Battery costs for vacuum tube aids generally vary more between individual users than between instruments.

Alterations in Dark Adaptation As a Function of Age.

R. A. McFarland and M. B. Fisher, *Harvard School of Public Health, Boston, Massachusetts, and Fresno State College, Fresno, California.*

This study relates to the ability of normal human subjects to see at low levels of illumination following exposure to a bright light. By means of a Hecht Adaptometer, approximately 250 males between the ages of 20 to 60 years of age were exposed to an illumination of 1,500 millilamberts for three minutes. The recovery process in the retina was followed by obtaining thresholds for minimum light sensitivity about every two minutes for a period of ten minutes (cone or color vision) and approximately every three minutes until 30 minutes had elapsed (rod or night vision).

Mean thresholds of age subdivisions of the sample studied have been shown to be significantly different. At the end of the thirty-minute test period the group 40 years old and over had a threshold 0.4 log unit (250 per cent) higher than the group 20 to 24 years old.

To learn whether the rate of dark adaptation was related to age, straight lines were fitted, by the method of least squares, to plots of the logarithm of the threshold against the logarithm of the time, and to plots of the logarithm of the threshold against the square root of the time. Both plots were reasonably well fitted by straight lines during the early part of both the cone and rod adaptation curves. Tests of the significance of the difference between mean slopes for the several age groups indicate that there is a real age trend in the rate of both cone and rod adaptation.

The conclusions to be drawn from this study are as follows: (1) There is a consistent decline in ability to see at low levels of illumination with increasing age under the conditions of this experiment; (2) the rate of adaptation and the final threshold level reached are both related to age; (3) the changes are quite marked in the older subjects and are believed to be related to certain basic but unknown physiologic functions in the retina; (4) these findings are of practical significance in helping to explain the difficulties experienced by subjects over 55 to 60 years of age in driving or flying at night.

Problems and Potentials of Professional Retirement.

S. L. Pressey, *Ohio State University, Columbus, Ohio.*

The paper brings together material from (a) a systematic survey of retirement plans and activities of older psychologists, (b) a survey of professional organizations regarding their provisions for retirement activities of their members, and(c) case studies of retired professional people in a midwestern city, in an effort to determine any trends, or needs for planning.

It seems clear that the majority of professional people desire some continuance of professional activities, after retirement—although there are interesting exceptions. It seems also clear that professional organizations and institutions of higher education have done almost nothing to support such continuance. Some continuance is usually feasible in medicine, law, and engineering. In some fields (such as biology) sundry institutes, state boards, and other agencies have made use of emeriti. Some university departments were found giving fine support to their emeriti, such as by making available some office space and clerical help; others seemed almost completely to forget them. Emeriti may be especially competent for certain tasks. Thus one kept records of the alumni of his department, most of whom he knew personally, another wrote a history of his science; the Gerontological Society appropriately includes a substantial number of emeriti from various fields, some of whom are making major contributions to its work.

Opinion seemed for tapering and against arbitrary retirement ages; valuable suggestions in these connections were offered.

It is suggested that retirement policies and opportunities might well be a matter for systematic consideration by the Gerontological Society.

The Distribution According to Age of Psychologic Measures Dependent Upon Organic Brain Functions.

R. M. Reitan, *Department of Surgery (Section of Neurological Surgery), Indiana University School of Medicine, Indianapolis, Indiana.*

In order to investigate the distribution with respect to age of certain psychologic measures related to organic brain functions, 50 brain damaged subjects were individually paired with neurologically "normal" persons on the basis of color, sex, age, and education in Experiment 1. In Experiment 2, 180 brain damaged and 101 neurologically "normal" subjects were employed. Halstead's tests for psychologic effects of brain damage were individually administered. Statistical comparisons were made of mean differences for the paired groups of 50 patients. The mean values were plotted according to age for the remaining two groups. In addition, r and eta coefficients between age and test results were calculated.

Highly significant differences between the paired brain damaged and control groups were obtained on all measures except two. In plotting the results according to age, the brain damaged patients showed impairment at all age levels and low correlations of test results with age. The neurologically "normal"

subjects gave adequate results up to age 45, but from this point on the curve definitely broke in the direction of impairment. Correlations between age and test results were much higher for the neurologically "normal" group than for the brain damaged group.

The results indicated (1) high sensitivity of Halstead's battery to the effects of brain damage, and (2) a distinct tendency for neurologically "normal" persons to show some impairment on the tests beginning at age 45. These results may have some relation to the peak of chronic diseases at about this age and may represent the effects of beginning brain changes. If so, the measurements may eventually have particular significance for preventive geriatrics.

The Role of Adult Education Administrators in Organizing Programs for Senior Citizens.

A. SALAMONE, *Adult Education Center, St. Louis University, St. Louis, Missouri.*

A major national problem is faced by our adults today because we refuse to extend the educational and informational processes beyond graduation. It is imperative that adults continue to study and to learn. We are living in what is probably the most complicated age of human history—merely to survive and function normally requires today many times the knowledge required a decade or two ago. The adult education administrator should assume leadership in organizing programs in his community that will prevent the mind from rusting away with disuse. There is a large majority of college graduates who drop dead mentally, as it were, once the four-year course is completed. Undergraduates in school should be taught "not only to learn, but learn how to continue to learn." Education, being the unfinished business that it is, cannot protect anybody too far in the future in this world of drastic change and development.

It is no wonder that we have the problems that we are faced with today in respect to our present aged; knowledge is being developed at a cyclonic pace, but is being implanted in men's minds at a comparative snail's pace.

The adult educator is aware of the baffling problems we are surrounded with in metropolitan district government, juvenile delinquency, congressional investigation of rights and wrongs, the hydrogen bomb, an impossible traffic situation, and another possibility of a world war started by the Communists over in Asia.

The understanding of these and many other problems will keep our aging population's minds, active, alert and in full use.

This paper will also explain the method to organize centers that meet the educational and recreational problems of the aging and the aged.

Section on Clinical Medicine.

Blood Studies of the Aged.

OUIDA D. ABBOTT, *University of Florida, Gainesville, Florida.*

Blood studies were made on 306 men and women 60 to 91 years of age, a group composed primarily of retired ministers, their wives, social workers, and teachers. Similar studies were made on 428 school children, 6 to 12 years; 244 high school pupils, 13 to 18 years; 241 college students, faculty members, non-academic personnel, and housewives, 19 to 50 years of age. All were apparently in good health and had no signs of acute infections or gross dietary deficiencies.

The highest mean hemoglobin values were those in subjects 60 to 91 years, 14.1 Gm. for men and 13.7 Gm. for women, and the lowest in the children, 12.7 Gm. and 12 Gm., respectively. There were no significant differences in hemoglobin levels of males and females in any age group. Only slight variations occurred in total erythrocytes, but again the oldest had the highest, 4.5 million, while the adolescents had the lowest, 3.6 million. The children had the highest total number of leucocytes, although averages of all groups were within the normal range. In the differential counts, the highest percentage of mature granulocytes, 55 per cent, was found in the oldest subjects and the lowest, 37 per cent, in the children.

From the response of approximately 50 per cent of the subjects with low hemoglobin values or low total red cells to hematinic treatment it was concluded that these low values were due to dietary deficiencies in blood forming constituents and were not related to the aging process.

Serum Lipoproteins in Older Individuals.

P. G. ACKERMANN, G. TORO, and W. B. KOUNTZ, *St. Louis Chronic Hospital and Division of Gerontology, Washington University School of Medicine, St. Louis, Missouri.*

Using the zone electrophoretic method, which is described briefly, the serum lipoproteins were studied in a number of middle-aged and elderly individuals and the results compared with those found in young adults. In the latter the lipoproteins were divided into 3 main fractions labelled alpha, intermediate, and beta fractions, which contained approximately 30, 10, and 60 per cent, respectively, of the total serum cholesterol. In a number of male subjects, whose average age was 51 years, and all of whom had definite evi-

dences of cardiovascular disease, abnormal curves were obtained with an increased percentage of cholesterol in the intermediate fraction (average of 26 per cent). In a number of older males, also with cardiovascular disease, the intermediate fraction was not as high, but the percentage in the beta fraction was increased to an average value of 78 per cent. Elderly individuals with minimal arteriosclerosis had lipoprotein curves not differing greatly from those found in younger adults. In some instances the distribution of lipoproteins could be correlated with the clinical state of the subjects. Changes in the lipoprotein curves with therapy were also noted and will be discussed.

Utilization and Protein Sparing Action of Carbohydrates in the Aged.

A. A. ALBANESE, R. A. HIGGONS, LOUISE ORTO, and JOAN ROSSY. *Nutritional Research Laboratory, St. Luke's Hospital, New York, New York.*

The rate of utilization of sugars in 51 fasting individuals (5 to 89 years) was studied in terms of blood sugar levels attained following the oral administration of tests doses (1 Gm./Kg.) of various sugars. These measurements showed that the utilization of dextrose decreases markedly with age, whereas the utilization of fructose is only slightly affected by the age of the individual. In both young and old subjects the rate of utilization of invert sugar and sucrose was greater than that of dextrose, but it was not as great as that found for fructose alone.

In a subsequent study of 96 fasting subjects (5-81 years) the effect of test doses of the sugars on the metabolic N pool was determined in terms of the changes induced in one hour in the blood amino N levels. The resulting data revealed that whereas the more readily utilized fructose makes an appreciable positive contribution to metabolic N pool, the less readily utilized dextrose does not.

These findings carry the suggestion that fructose or fructose-containing products are the sugars of choice for the aged in that they may provide a ready source of energy and an optimal protein-sparing effect.

The Practice of Geriatrics.

L. L. AMATO, *Fort Lauderdale, Florida.*

An outline will be given of suitable office facilities and procedures for physicians specializing in geriatric medicine. The procedures applicable to examination of geriatric patients will be discussed and the relation of the geriatrician to the community will be reviewed.

Electroencephalographic Findings in a Study of Aged Patients with Cardiac Disease.

L. F. BISSELL and W. D. OBRIST, *Moosehaven Research Laboratory, Orange Park, Florida.*

Clinical and electroencephalographic observations were made on 41 male subjects between 66 and 91 years of age. Twenty of these individuals had heart disease, as determined by a medical history, physical examination, and laboratory tests, including chest x-ray and electrocardiogram. Twenty-one individuals with a similar mean age, who showed no evidence of cardiac disease, served as controls. Care was taken to exclude those subjects with a history of epilepsy, severe head injury, or evidence of cerebral vascular accident.

When compared with normal subjects, the electroencephalograms of patients with cardiac disease had a significantly slower dominant (alpha) rhythm. The mean alpha frequency for the control group was 9.4 c/sec., as compared with 8.3 c/sec. for the cardiac group. The incidence of slow (delta) wave activity was much greater in the group of cases with heart disease. More than half of the patients with abnormal electrocardiograms had a slow alpha rhythm or delta waves in their EEGs.

The significance of these findings is discussed in terms of the probable effect of cardiocirculatory dynamics on cerebral circulation and metabolism as reflected in the EEG. Evidence is presented that the electroencephalogram provides a useful tool in assessing the role of cardiac disease in the production of states of disturbed cerebral function. Typical cases are presented.

"Deaging," Some Principles and Methods.

C. W. CRAMPTON, *New York, New York.*

Intermittent Claudication Treated With Ultrafaradism.

G. R. CRISLER, *Winter Park, Florida.*

Twenty patients with intermittent claudication were treated with the Ultrafaradic Impulse Generator. From 5 to 50 daily treatments were given in the various cases. No attempt was made to classify the cases as to etiology before treatment. The results were judged by increase in claudication time and distance. The results showed definite improvement in 10 cases, some improvement in 6 cases, and failure of treatment in 4 cases. In the first group the claudication time was increased significantly or pain on exercise disappeared completely. The intermediate group showed less marked improvement and the third group no improvement. The series was not large enough to furnish untreated control cases, if in fact this is at all possible. The benefits must be assessed in terms of comparison with results obtained in untreated cases as a whole and in cases treated by other methods. An analysis of the 3 different groups of patients would seem to indicate that ultrafaradic physiotherapy is of most value in those cases in which there is a sizable functional component and that it is of less value in cases in which the organic component is prepotent. There is, how-

ever, no absolute relation between severity of symptoms and efficacy of treatment. And there is some evidence to suggest that the organic component, as well as the functional component, may be reduced to some extent by ultrafaradic physiotherapy.

Atherosclerosis in the Intramural as Compared to Extramural Coronary Arteries.

J. C. EDWARDS, C. BURNSIDES, R. SWARM, and A. I. LANSING, *Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.*

Among 276 hearts examined in a series of autopsies, only 15 instances of intramural coronary arteries were observed. All but 1 of these had 1 intramural portion with atheromata and narrowing of the lumen. The other extramural coronary arteries in these hearts also had atherosclerotic involvement. Eight had marked involvement, 5 had moderate, and 2 had slight arteriosclerosis. One was in the left circumflex branch and was occluded by a thrombus in the intramural portion. Eleven were in the left anterior descending branch; only 1 involved the right coronary artery. We found approximately 1 out of every 17 human hearts (5.8 per cent) had an intramural coronary for some portion of its proximal or mid course. Microscopic examinations, degrees of involvement, and other data were analyzed. Elastic tissue studies were performed on some of the specimens. The data and questions relating to the problem will be discussed.

In these observations there was no evidence to support the concept, (Geiringer: The Relation of the Mural Coronary Artery to Arteriosclerosis. *Am. Heart J. 41:* 359, 1951.) that covering of a coronary artery by heart muscle during all or a part of its main course protects the artery from degenerative abnormalities.

The Incidence of Atherosclerosis in a Random Sample of a Union Population.

F. H. EPSTEIN and E. P. BOAS, *Research Division, Sidney Hillman Health Center, New York, New York.*

The incidence of manifest atherosclerosis in a random sample (499 men and 396 women) of a union population of garment workers aged 40 years and over was studied. The union has some 30,000 members. Criteria for diagnosis were the demonstration of coronary artery disease, peripheral or cerebral vascular disease, and roentgen demonstration of calcification of the thoracic or abdominal aorta.

The over-all frequency of atherosclerosis is shown in the following table.

	Incidence—per cent	
Ages	Women	Men
45 to 49	7.7	11.1
50 to 59	25.7	30.8
60 to 69	58.1	47.9
Total	25.8	34.3

A breakdown by site of the lesion shows the following percentage incidence.

	Women	Men
Coronary disease	2.8	11.6
Peripheral artery disease	0.5	3.2
Aortic calcification with other atherosclerotic lesions	24.5	25.4
Aortic calcification—solitary	22.5	19.8

Aortic calcification begins to show on roentgen films at about age 45 in some 8 per cent of men and women. In the sixth decade the incidence is about 25 per cent in both sexes. After age 60 some 37 per cent of men and 55 per cent of women exhibit aortic calcification, chiefly in the abdominal aorta.

The average total serum cholesterol in milligrams per 100 ml. was:

No atherosclerosis		Atherosclerosis present	
Women	Men	Women	Men
234	229	263	233

Aortic calcification—solitary	
Women	Men
264	230

Tables showing the frequencies of the several lesions, together with serum cholesterol and phospholipid levels in successive quinquennia will be presented.

The data demonstrate the progressive parallel increase in frequency of atherosclerosis with age in both sexes. When aortic calcification is included as a diagnostic criterion, atherosclerosis is as common in women as in men, although coronary disease is only one quarter as frequent in women. There is no close correlation between the level of serum cholesterol and the frequency of atherosclerosis at various ages. The different localization of atherosclerosis in the two sexes suggests that local factors must be operative in addition to metabolic ones.

Physiologic Reserve in the Chronically Ill and Aging.

M. B. FERDERBER, *University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.*

For the past eight years the writer has been interested in the physiologic mechanism which permits patients (particularly the aging) who are bedfast and disinterested in their surroundings for periods ranging from days to years to return to varying degrees of physical and mental independence.

Prior to the beginning of a "reactivating" venture at Woodville and Mayview (Allegheny County Institution District) with totally bedfast individuals, complete laboratory and clinical data were collected and various activities, previously omitted, were then started. Other than increase in heart and respiration rate, virtually no clinical changes were noted except, of course, voluntary motions of parts. From a laboratory standpoint, changes were obvious but not startling. Changes of personality were considerable and consisted of increased general interest and a desire for

social contact. The cause of these improvements cannot be definitely stated.

This paper is offered to prompt discussion on the subject of the mechanism responsible for the observed restoration of physical and mental activity.

A Geriatric Clinic in a General Hospital.

L. FRIEDFELD, *New York, New York.*

Many elderly people seek permanent institutional care because of relatively minor or transient physical and emotional illnesses, or their inability to resolve socio-economic problems. A geriatric clinic in a general hospital may help these people and those with chronic disease to remain within their own community on an ambulatory basis.

In March 1954 a holistic geriatric program was started in the Out-Patient-Department of the Beth Israel Hospital of New York. It seeks to restore and maintain maximum physical, emotional, and social well being.

In addition to geriatrically oriented physicians, psychiatrist and full-time case worker, all the facilities of the general hospital and co-operating independent community agencies are available.

The work-up includes a complete personal and social history, determination of abilities and aptitudes, evaluation of emotional status, and a complete physical examination with utilization of necessary specialty consultations and laboratory aids. A total diagnosis and a program of management are then determined at a combined geriatric staff conference. When present, a spouse is included in the survey.

In addition to medical follow-up, available facilities include dietary counseling, dental care, physical medicine and rehabilitation, occupational therapy and retraining, recreation and activity programs, and guidance to channels for economic assistance. A group psycho-therapy program is also contemplated.

Thus far the patient reaction has been one of responsive appreciation for unusual interest and thoroughness. The staff members consider the program a necessary, effective, and rewarding experience.

Lipoproteins, Aging, and Coronary Artery Disease.

F. W. GLAZIER and J. W. GOFMAN, *Donner Laboratory, University of California, Berkeley, California.*

Coronary artery disease is regarded as a chronic accumulative disease rather than an acute process. Further, it is believed that examination of the coronary arteries in the living population would reveal that there exists a continual gradation in the severity of the disease, wholly independent of whether or not clinical manifestations are present. In view of these considerations, the purpose of this work is to evaluate quantitatively the amount of accumulated coronary artery disease present in living individuals.

The term accumulated coronary artery disease implies that the disease is and has accumulated at some rate, operating over some time. The hypothesis presented defines the rate of accumulation of coronary disease as proportional to the "effective" concentrations of certain serum lipoproteins. In particular, the rate is defined as proportional to $1.0 \times$ (Serum concentrations of Standard S_f0-12 lipoprotein) $+ 1.6 \times$ (Serum concentration of Standard S_f12-400 lipoprotein). The sum of these two products is termed α, and the rate of accumulation is then $k\alpha$, where k is a proportionality constant relating rate of accumulation with effective concentration. With the rate of development of coronary artery disease defined, the accumulated coronary artery disease (A.C.D.) can be defined as the rate $\times$ the time this rate has operated. Symbolicly A.C.D. $= \int k\alpha \, dt$.

The validity of this hypothesis concerning accumulation of coronary artery disease must be tested. Since, to our knowledge, there is no independent direct method, recourse must be taken to an indirect method. From A.C.D. measurements it is possible to predict incidence rates of clinical manifestations, and thence mortality rates from coronary disease. These predicted rates have been computed, and compared with established actuarial data.

Results of Reserpine Therapy in Hypertension.

R. HARRIS, *Ann Lee Home and Albany Medical College, Albany, New York.*

The results of a year's study of the effects of reserpine therapy in hypertensive patients, including elderly subjects, will be presented. The administration of reserpine produced a triple response which included a gradual fall in blood pressure, definite slowing of the heart rate, and sedation. The most dramatic blood pressure responses occurred in young, tense individuals with labile hypertension and rapid pulses. Elderly hypertensive patients demonstrated a slow blood pressure drop of lesser magnitude which did not provoke untoward symptoms or signs referable to the lowered pressures. Patients with advanced malignant hypertension and/or generalized atherosclerosis showed no constant significant response to the administration of reserpine alone.

A decrease in the heart rate frequently accompanied the fall in blood pressure. The majority of the patients in whom reserpine proved effective developed heart rates of 50 to 60 beats per minute. Elderly patients with slow heart rates showed rates from 40 to 50 beats per minute under the influence of reserpine. One patient had a heart rate of 38 beats per minute with sinus rhythm. This bradycardiac effect appeared related to increased vagal activity since atropine caused the heart rate to accelerate.

The most constant effect of reserpine was its mildly sedative action in small doses which was of value in reducing the emotional and mental tensions of all patients, including the aged. No significant toxic effects occurred except for drowsiness, tiredness, and exhaustion with large doses of the drug.

The majority of the patients treated were residents of an old age home. All patients received placebo and reserpine tablets alternately. Oral and sublingual routes of administration were equally effective.

Radioactive Iodine in the Treatment of Cardiac Disease in the Elderly.

J. E. KEARNS and J. D. CROFT, *Departments of Surgery and Medicine, Northwestern University and Evanston Hospital, Evanston, Illinois.*

A review of 45 patients over 65 years of age in whom a chronic auricular fibrillation was noted showed no evidence of hyperthyroidism other than increased radioactive iodine uptake in the thyroid at the end of twenty-four hours and elevated protein-bound iodine. These patients were treated with radioactive iodine. The dosage has been variable and the response has been excellent.

The Effects of Hypotensive Agents on Patients with Cerebral Vascular Insufficiency.

J. KLEH and J. F. FAZEKAS, *District of Columbia General Hospital, Washington, D. C.*

The employment of the more recently developed hypotensive drugs—hexamethonium, 1-hydrazinophthalazine hydrochloride, and reserpine—in elderly patients with hypertension and cerebral vascular insufficiency has been both advocated and discouraged. Rational usage of such drugs must be based on the measured alterations in cerebral hemodynamics produced by such therapy coupled with the observed clinical effects.

During the past two years we have conducted such a study at an institution for the care of the aged. Most of the subjects in this study have had courses of therapy with two of these agents, and it has been possible to study a small group through courses of all three hypotensive drugs

Each subject received a baseline evaluation including history, physical examination, complete blood count, urinalysis, blood urea nitrogen, electrocardiogram, and determination of cerebral blood flow, cerebrovascular resistance, and cerebral metabolic rate. These were repeated while under therapy with each drug. The effects of acute and chronic reduction of blood pressure were studied during the administration of hexamethonium chloride. The effects of the other drugs were studied only after the mean arterial pressure had been reduced for some time to approximately normal levels.

The acute reduction of blood pressure to normotensive levels with hexamethonium in most instances resulted in acute cerebral vascular insufficiency and in a marked fall in cerebral blood flow. With chronic reduction in pressure, about half of the subjects demonstrated increased manifestations of cerebral insufficiency despite no significant change in cerebral blood flow.

A satisfactory blood pressure reduction was obtained with reserpine (Serpasil), but there was no change in blood flow or metabolic rate with the high doses employed. No improvement was noted in the manifestation of cerebral vascular disease in any of the subjects; in fact, their apathy and drowsiness increased in many instances.

1-Hydrazinophthalazine (Apresoline) therapy resulted in an effective reduction in blood pressure, a significant increase in cerebral blood flow, and a significant decrease in cerebral vascular resistance. Clinical improvement was evident in the majority of subjects on this drug and definite reversal followed placebo substitution.

Dihydrogenated Ergot Derivatives in Cerebral Arteriosclerosis.

T. D. LABECKI, *Mississippi State Board of Health, Jackson, Mississippi,* and C. L. BUSBY, *Mississippi State Hospital, Whitfield, Mississippi.*

Two groups of 15 white males each were chosen from among permanent inmates of Mississippi State Hospital. All of them had suffered for a number of years from the chronic brain syndrome, cerebral arteriosclerosis with psychotic reaction. Their mental status had reached a certain established degree, and the level was well known to their nursing and medical entourage. Group II differed from Group I in the severity of the syndrome, all 15 of them having reached a definitely lower level of cerebration when compared with the first group.

Because of the apparent hopelessness as to any spontaneous improvement in the syndrome, it was decided to conduct a "blind" study, administering subcutaneously daily for 60 days one of 5 coded medications, the contents of which were known only to the medical directors of a cooperating pharmaceutical concern. An unknown number of the 5 lots contained an equimixture of Dihydroergocornine, Dihydroergokryptine, and Dihydroergocristine; the remaining lots were normal saline.

In both Group I and II each lot of medication was administered to 3 patients. There was no change of regime, no supplementary therapy, and no change of environment. The condition of the patients was evaluated periodically by a team of 2 physicians and 2 nurses, the latter attending the patients constantly. Definite criteria of response were decided upon prior to medication. The response, if any, was to be des-

ignated 1 plus, 2 plus, or 3 plus; lack of response was indicated by a minus sign.

Marked improvement was noted among the patients in Group I receiving dihydrogenated ergot derivatives; the patients receiving placebo failed to show any improvement. No appreciable response to either of the substances administered was observed in Group II. Charts showing the degree of response have been prepared and would be available to the attending members of the Society.

The Effect of Age Upon the Relative Gonadal and Adrenocortical Activity of the Male.

S. PEARSON and T. H. MCGAVACK, *New York Medical College, Metropolitan Hospital Research Unit, Welfare Island, New York, New York.*

Urinary neutral 17-ketosteroids excreted by young and aged males were chromatographically fractionated. Evidence that different fractions of steroids originated in either the gonads or adrenal cortex was obtained by the chromatographing of crystalline steroids known to be present in urine and believed to arise in the gonads or adrenal cortex, e. g., androsterone, epiandrosterone, and 11-hydroxyetiocholanolone. Further indications as to the source of the steroids in the various fractions were found by examination of the chromatograms of urinary 17-ketosteroids excreted by hypo- and agonadal males. The data showed that the percentage of urinary neutral 17-ketosteroids of gonadal origin decreases with increasing age. Such data, obtained by a chromatographic procedure, may provide a quantitative measure of relative gonadal and adrenocortical activity which would be much more informative as to endocrine status than measurement of total 17-ketosteroids and corticosteroids.

A New Antidepressant (M.R.D.-108) in Geriatrics

J. POMERANZE, *New York Medical College—Flower and Fifth Avenue Hospitals, and Bird S. Coler Memorial Home and Hospital, New York, New York.*

Premature retirement and the fear of impending deterioration and death often create a serious mental depression in the older but otherwise organically fit individual. It is difficult to inspire them to continue normal activities. Various amphetamine combinations with phenobarbital have until recently constituted the sole organic approach to this problem. A new drug M.R.D.-108 (α-(2-piperidyl) benzhydrol hydrochloride) has suggested itself as valuable for stimulating a greater zest for living in the older depressed patient.

M.R.D.-108 is effective in small doses (2 mg.) and its duration of activity is at least 24 hours. The necessity for repeated doses and constant observation of drug taking is obviated. In therapeutic doses there are few side effects when its use is limited to the depressed or tired patient.

Little effect was noted on appetite in the thin person. A better attitude appeared to permit the obese subject to maintain dietary control and lose weight. The depressed patient displayed an increased alertness and a better interest in routine activities. This was quickly apparent and was well maintained throughout the day without any interference with sleep.

An additional advantage was that no tolerance developed. Urine examinations, blood counts, and liver function tests remained normal during the observation periods.

Management of Peripheral Arterial Disease in the Aged.

S. S. SAMUELS, *New York, New York.*

Methods of recognition of peripheral arterial disease in the aged according to modern methods and details of treatment are outlined. Changes in ideas of treatment which have occurred during the past thirty years, including ambulatory, hospital, and surgical care are discussed.

Incidence of Diseases of the Gastrointestinal Tract Among Mentally Ill Patients Over 60 Years Old.

G. STRASSMANN and M. ASEKOFF, *Laboratory of the Metropolitan State Hospital, Waltham, Massachusetts.*

Diseases of the gastrointestinal tract were found in 133 of 204 mentally ill patients over 60 years old. There were 103 patients with and 101 patients without senile changes in the brain; 74 senile and 59 nonsenile patients showed one or more of the following diseases:

acute intestinal obstruction	6	senile,	7	nonsenile
acute or chronic peptic ulcers	13	"	18	"
enterocolitis	32	"	18	"
malignant tumors	6	"	4	"
diverticulosis	32	"	18	"
esophagogastromalacia	11	"	7	"

Of the 74, respectively 59 patients were:

obese	18	senile,	18	nonsenile
moderately nourished	10	"	17	"
emaciated	46	"	24	"

Weight of brain	under	1100	Gm.:	24	senile,	10	nonsenile
" " heart	"	350	"	44	"	24	"
" " spleen	"	100	"	32	"	18	"
" " liver	"	1100	"	35	"	25	"
" " kidney (each)	"	120	"	44	"	31	"

More than 50 per cent of senile and nonsenile patients had arteriosclerosis of coronary and cerebral arteries and the aorta.

Gastrointestinal diseases, especially enterocolitis, diverticulosis, and peptic ulcers, were thus found to be frequent in autopsies of mentally ill patients over

60 years old. Senile and nonsenile patients of this age group showed often malnutrition, atrophy of internal organs, cardiovascular disturbances, and a lowered resistance against any noxious agent. These facts explain the frequent incidence of damage to the gastrointestinal tract. Malignant tumors were relatively rare in this material.

Supported by Grant M-710, National Institute of Health, U. S. Public Health Service.

The Ballistocardiogram in the Aged.

S. STORSCH, *Jacksonville, Florida.*

Medical Responsibility for the Older Person.

F. C. SWARTZ, *Lansing, Michigan.*

Fractures of the Neck of the Femur in the Aged.

S. E. ZIFFREN, M. S. GOLDSTEIN, and C. L. BEYE, *Department of Surgery, State University of Iowa, College of Medicine, Iowa City, Iowa.*

A review of the results of the treatment of patients with fracture of the neck of the femur treated at the University Hospitals of the State University of Iowa during the years 1940 to 1952 forms the basis of this report. A total of 233 patients, 175 of whom were over 65 years of age, have been studied. The end results are based upon roentgenograms, return examinations, and questionnaires to the patient or his family and the family physician. The hospital mortality rate of those operated upon was 14.9 per cent in patients over the age of 65. Discounting those who died prior to surgery and in the immediate postoperative period, and those who died too early for evaluation, 122 patients were available above the age of 65 for this study. Of these, 19 were not available for follow-up study, leaving a total of 103. Of these 74.7 per cent are walking. These figures will be further subdivided into various groups as walking with cane, without cane, those who are permanent invalids, etc. In addition these figures will be compared to those obtained in patients under the age of 65 treated for the same type of fracture.

In spite of the recent depressing reports as to the eventual rehabilitation of the elderly group of patients with this type of fracture, it seems this procedure is quite effective and worth while.

BOOK REVIEWS

HOW TO HELP OLDER PEOPLE, by Julietta K. Arthur, J. B. Lippincott Company, Philadelphia and New York, 1954, 383 pages, 102 pages of appendices, 10 pages index, $4.95.

Books on the problems of aging are multiplying rapidly, more and more of them dealing with immediate practical problems. Among them are Buckley's *The Retirement Handbook—A Complete Planning Guide to Your Future*, Stern and Ross' *You and Your Aging Parents*, Public Affairs Pamphlet No. 131 *When You Grow Older*, to mention only a very few. Some are intended for the older person himself; others for those having concern for him.

How to Help Older People, by Mrs. Arthur, is perhaps the most practical of all. Technical material by specialists in medicine, psychology, and social work are discussed in lay language with numerous illustrations. It, too, is one of the most comprehensive books. It includes the everyday type of problem which the aged presents to the younger,—friends and relatives. Among these problems are, getting along with older people; normal old age; preparation for the later years; employment, retirement, and leisure; living arrangements; community care for the chronically ill; and others.

Although the book is designed for the family with an aged member and discusses "what to do for and with older people who are close to you," it is one of the most practical for the older person himself, for this is the type of information he needs to realize his part in the adjustment process. It also provides practical help for the younger in the preparation for his own old age.

The book is almost a handbook in its practicability. To make it so, the author has drawn on vast amounts of scientific and other literature not easily available, and she has filled the 102 pages of appendices and 10 solid pages of index with substantial guidebook materials. The appendix to chapter 15, "What's New for the Old," will illustrate, for there are listed the following: 1) a directory of 48 national organizations concerned in some respect with the lives of the aged, 2) 9 motion pictures on aging problems, and 3) 5 sources of tape recordings and records suitable for radio stations or discussion groups. A selective bibliography by chapter in the appendix provides further profitable reading on the problems discussed.

W. H. REALS
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Washington University

WHEN PARENTS GROW OLD, by Elizabeth Ogg, Public Affairs Pamphlet No. 208, The Public Affairs Committee, Inc., New York, 1954, 28 pages, paper bound, 1-9 copies, 25¢ each, discounts on larger quantities.

This pamphlet brings to at least four on the problems of aging, published by the Public Affairs Committee. The others have been: *When You Grow Older, Live Long and Like It*, and *Getting Ready to Retire*.

Increasing longevity, the fact that more than 1/6 of those 65 and over are supported by children or relatives, and changes in living arrangements make old age everybody's problem. Older persons' needs parallel closely the needs of the younger: adequate food, clothing, and shelter; desire to be useful and active; to maintain status; to have affection shown; and to possess freedom and independence.

Three principal problems are discussed: preserving independence as long as possible by suitable living arrangements and attention to the aging parent, foster homes and homes for the aged, and the community's responsibility.

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ALTERN UND KRANKHEIT, 2nd edition, by Max Bürger, Georg Thieme Verlag, Leipzig, 1954, 600 pages, 40 RM.

The second edition of M. Bürger's monograph on problems of aging contains 187 more pages and 115 more illustrations than the first edition of the book published in 1947. In spite of the increase in size, the character of the book remains essentially unchanged. The main aspect of the book consists of a review of research work carried out by Bürger and his associates at the medical university clinic in Leipzig. The first section of the book, 282 pages, deals with general aspects of aging, whereas the second section, 292 pages, is devoted to problems related to geriatrics.

In addition to an exhaustive and careful description of the results of research work performed at the Leipzig institute the book contains quite extensive references to other German publications on the aspects of aging. Studies by English and American investigators are discussed only incidentally. It should be pointed out in this connection that, as mentioned in the introduction to the book, it has not been Bürger's intention

to provide a complete review of the existing literature on gerontologic subjects. In the reviewer's opinion the limitation of the book mainly to a consideration of continental European research work in gerontology would in fact seem to be an advantage to American readers, who have easy access to the British and American literature in the field. Although current lists of gerontologic literature references attempt to include the European literature on gerontology, these lists are not complete and in particular usually do not give references to doctoral theses on gerontologic subjects. Such references are contained in Bürger's monograph, which therefore constitutes a valuable supplement to American textbooks and literature lists on gerontology. There are several misprints in the book, particularly in the literature references, but these are not of a disturbing character.

Although the philosophic approach, which characterizes some of the sections in Bürger's monograph, probably will not appeal to most American readers, the many concise, numerical statements in the book and the numerous graphic illustrations should be valuable to research workers in the field of gerontology and geriatrics. The second edition of Bürger's book can therefore be recommended to American gerontologists.

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HOUSING THE AGING, edited by Wilma Donahue, University of Michigan Press, Ann Arbor, 1954, 280 pages, $3.75.

The Fifth Annual University of Michigan Conference on Aging (there have now been seven) was designed to bring together the best information that existed on housing and living arrangements for older people and to stimulate interest among key groups in providing living facilities for those who wish to remain functional up to the limit of their capacities.

That the Conference was successful in attracting representatives of several important groups is attested by the participation of builders, financial experts, medical people, social scientists, city planners, architects, social workers, and housing and institutional administrators. All who participated formally were invited because of their experience and imagination; the wisdom of the choices is reflected in the contributions which form the major part of the book.

The section dealing with communal facilities is the most authoritative because most American experience lies in this area. Contributions on the housing interests and needs of the aging reveal close attention to the expressions of older people themselves, while those on community services and maintenance of standards reflect the most advanced expert thinking.

The knotty problem of financing housing for older people is approached from several angles. There seems to be a general conviction that there are no insurmountable obstacles once the proper interests set their minds to the problem. Dr. Donahue's final, survey chapter indicates that not many have accepted the challenge.

Fortunately, there is evidence that interest is growing. If the guide-lines set up in *Housing the Aging* are read and followed, it should not be long before real progress can be reported.

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BOOKS RECEIVED

Books received since May 1, 1954, are acknowledged in the following list.

Altern und Krankheit, 2nd edition, by Max Bürger, Georg Thieme Verlag, Leipzig, 1954, 600 pages, 40 R.M. (reviewed in this issue, page 488).

Coronary Heart Disease in Young Adults, A Multidisciplinary Study, by Menard M. Gertler and Paul D. White, Harvard University Press, Cambridge, 1954, 218 pages, $5.00.

Gezondheidsproblemen Bij Bejaarden (Health Problems of the Aged). Resultaten van een Sociaal-Geneeskundig Onderzoek bij 3000 Personen van 65 Jaar en Ouder in de Stad Groningen, by Robert Jacques van Zonneveld, Van Gorcum & Co., N. V., Groningen, 1954, 248 pages, paper bound.

How to Help Older People: A Guide for You and Your Family, by Julietta K. Arthur, J. B. Lippincott Company, Philadelphia, 1954, 500 pages, $4.95 (reviewed in this issue, page 488).

Impairment Study, 1951, Society of Actuaries, 1 Madison Avenue, New York 10, New York, 1954, 300 pages, $7.50.

Meaning of Social Medicine, by Iago Galdston, Harvard University Press, Cambridge, 1954, 137 pages, $2.75.

New York City's Senior Citizens. Volume 1: Report of the Mayor's Advisory Committee for the Aged, October, 1949 to October, 1953, 26 pages. Volume II: Appendix, Report of the Mayor's Advisory Committee for the Aged, October, 1949 to October, 1953, 81 pages. Volume III: Report of the

Mayor's Advisory Committee for the Aged, December, 1953, 11 pages, mimeographed.

Newer Concepts of the Causes and Treatment of Diabetes Mellitus. Proceedings of the Symposium on Diabetes Sponsored by the New York Diabetes Association and held at Memorial Hospital and the New York Academy of Sciences, New York City, October 8, 1953, National Vitamin Foundation, Inc., 15 East 58 Street, New York 22, New York, 1954, 181 pages, paper bound, $2.50.

Older Women as Office Workers, Bulletin of the U. S. Department of Labor, Women's Bureau, No. 248, Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1954, 64 pages, paper bound, 25¢.

Peripheral Circulation in Man, G. E. W. Wolstenholme and Jessie S. Freeman, editors for the Ciba Foundation, Little, Brown and Company, Boston, 1954, 219 pages, $6.00.

Standards of Design, Housing for the Elderly, Massachusetts State Housing Board, Boston, 17 pages, paper bound.

When Parents Grow Old, by Elizabeth Ogg, Public Affairs Pamphlet No. 208, Public Affairs Committee, Inc., New York, 1954, 28 pages, paper bound, 1-9 copies, 25¢ each, discounts on larger quantities (reviewed in this issue, page 488).

INDEX TO CURRENT PERIODICAL LITERATURE

NATHAN W. SHOCK
Gerontology Section
National Heart Institute
National Institutes of Health

The subject categories are those in *A Classified Bibliography of Gerontology and Geriatrics* by Nathan W. Shock published by Stanford University Press, Stanford, California (1951). Only major headings are used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available, abstract references are given (*B.A.—Biological Abstracts; P.A.—Psychological Abstracts;* and *P.I.—Population Index*). Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the years 1900-1933*, 2nd Edition. For journals not listed, abbreviations were devised according to the general rules used in the above source. It is impossible to cover all journals and list all papers concerned with aging and the aged. Authors and publishers are requested to call attention to publications or to send reprints to the Gerontology Section, Baltimore City Hospitals, Baltimore, Maryland. The assistance of the Forest Park Foundation, Peoria, Illinois, in the preparation of these materials is gratefully acknowledged.

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Notice

The January, 1951, July, 1951, and January, 1952, issues of the Journal of Gerontology are now out of print. The Journal of Gerontology will be glad to purchase copies of these issues which are in good condition for $3.50; issues should be sent to:

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DECEMBER 28, 29, and 30, 1954

The program of the Sections of Psychological and Social Sciences, Clinical Medicine, and Social Work and Administration is published in this issue; the program of the Section of Biological Sciences was published in the July issue.

Information on exhibits may be obtained from Mr. I. L. Webber, Department of Sociology, University of Florida, Gainesville, Florida.

Reservations for rooms, luncheon meetings, and annual dinner should be sent, prior to December 15, to Mr. F. T. Adams, Jr., General Extension Division of Florida, University of Florida, 707 Seagle Building, Gainesville, Florida.